Protocol to Implement and Evaluate a Model Medical Surveillance Program for Occupational Asthma and to Characterize the Incidence of Occupational Asthma Associated with Toluene Diisocyanate Exposure in the Production Environment

A collaborative research and development program on occupational safety and health of the

National Institute for Occupational Safety and Health (NIOSH)**,** Centers for Disease Control and Prevention (CDC)

The American Chemistry Council (ACC) Diisocyanates Panel (Panel

List of Appendices

(Located after page 53)

Appendices #25, 26, 27, 28, 29, 31, 32, 33 are located on CD-Rom.

Abbreviations

ACC	American Chemistry Council
ACGIH	American Conference of Governmental Industrial Hygienists
CDC	Centers for Disease Control and Prevention
FEV1	Forced Expiratory Volume at One Second
FVC	Forced Vital Capacity
HPET	High Potential Exposure Tasks
ICG	Integration and Communication Group
IH	Industrial Hygiene
MOU	Memorandum of Understanding
NIOSH	National Institute for Occupational Safety and Health
OA	Occupational asthma
SEG	Similar Exposure Groups
SENSOR	Sentinel Event Notification System for Occupational Risks
STEL	Short-Term Exposure Limit
TDI	Toluene Diisocyanate
TLV	Threshold Limit Value
TWA	Time-Weighted Average

Glossary

Allergen – a substance that can stimulate specific responses in the immune system and on re-exposure causes an allergic reaction in sensitized humans.

Asthma – is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli.

Forced expiratory volume measured at 1 second (FEV_1) – the gas volume exhaled in the first second exhaling as hard and fast as possible, after maximal inspiration.

Forced vital capacity (FVC) – the total gas volume which can be exhaled, exhaling as hard and fast as possible after maximal inspiration

Medical Monitoring or Surveillance – the performance and analysis of routine measurements aimed at detecting changes in the health status of a population.

Job-exposure matrix – an assignment of specific estimates of exposure to a series of distinct job categories, for the purposes of estimating exposures for a defined population of workers.

Longitudinal study – the method of epidemiologic study in which a defined population (cohort) is evaluated repeatedly during a period of time, to assess changes in outcomes associated with interventions, exposures, or other risk factors.

Pulmonary function – the performance of the respiratory system in supplying oxygen to and removing carbon dioxide from the body by way of circulating blood and moving air in and out of the alveoli.

Similar Exposure Group (SEG) – a classification of workers who are expected to experience similar types, patterns, and levels of exposure and have similar potential for exposures.

Toluene diisocyanate (TDI) – toluene-2,4-diisocyanate or toluene 2,6 diisocyanate, an organic chemical used in a variety of applications such as elastomers, coatings, and adhesives.

TDI-induced occupational asthma – asthma caused by exposure to TDI in a working environment and not by factors outside the work environment

Work-aggravated asthma – pre-existing or concurrent asthma in which conditions at work have resulted in a clinically important worsening of lung function and/or respiratory symptoms, or the need for increasing dosages or types of medication.

Work-related asthma – asthma caused by exposures received in the working environment and not by factors outside the work environment.

Study Summary

Previous studies have demonstrated a causal relationship between workplace exposures to toluene diisocyanate (TDI) and the development of occupational asthma (OA). Early detection of respiratory sensitization to TDI, through medical surveillance and occupational clinical practice, is important in limiting health consequences and decreasing OA. Clinical assessment plays an important role in medical monitoring and requires both occupational history and objective measures (e.g., serial lung function measurement).

Each site which is participating in this study has had their own medical surveillance program, and these have varied from one another in data collection and recording procedures. The aim of this pilot study is to standardize medical evaluation and reporting across sites, while neither decreasing medical care over existing site practices nor interfering with ongoing clinical assessment and treatment of participants. This uniformity allows for the pooling of data across sites and subsequent hypotheses testing regarding the diagnosis and prevention of TDI-induced OA.

I. Background of Study

A. Introduction

Workplace exposures to diisocyanates, such as toluene diisocyanate (TDI), have long been recognized as capable of inducing asthmatic responses in some individuals exposed at high concentrations (Fuchs and Valade, 1951; Woodbury, 1956). Clinical aspects of the health effects of diisocyanate compounds, including asthma induction, have been recently reviewed (Redlich and Karol, 2002; Wisnewski and Redlich, 2001; Bernstein and Jolly, 1999). Based on surveillance data from a number of national and regional occupational asthma (OA) reporting systems, diisocyanates are the most commonly reported causes of OA among small-molecular-weight compounds (Meredith and Nordman, 1996; McDonald et al., 2000; Jajosky et al., 1999; Contreras et al., 1994; Provencher et al., 1997). As summarized later in this section, there is consistent evidence from surveillance systems in the U.S., U.K., Finland, and Canada, of declining occurrences in OA due to diisocyanates in general and TDI in particular. A review of longitudinal workplace studies also indicates that incidence rates of TDI-induced asthma have declined and, in recent years, have generally not exceeded one per hundred employees on an annual basis (Ott et al., 2003). These favorable trends appear to be related to a reduction in workplace exposures through engineering controls and changes in work practices.

Improvements in medical surveillance programs may provide an additional avenue for better management of the health risks associated with workplaces producing or using diisocyanates. Based on retrospective evaluation of a medical surveillance program introduced in Ontario, Canada in 1983, it has been suggested that the program contributed to a reduction in accepted compensation claims for OA and a less severe outcome for those persons diagnosed with diisocyanate-induced OA (Tarlo and Liss, 2002). Experience within one company with an active medical surveillance program also suggests a favorable outcome profile for OA cases based on reduction in the duration of symptomatic exposure (Ott et al., 2000).

Over the last several years, occupational health professionals from the National Institute for Occupational Safety and Health (NIOSH) and member companies of the American Chemistry Council (ACC) Diisocyanates Panel met to discuss ways of improving the management of health risks associated with occupational exposure to diisocyanates. These meetings, which included academic

experts and worker representatives, led to a Memorandum of Understanding (April 29, 2003) between NIOSH and the ACC Diisocyanates Panel to establish a collaborative research and development program (Program). The Program focused on studying the future occurrences of OA associated with TDI exposure in manufacturing facilities of U.S. TDI producers using a longitudinal approach and standardized exposure and medical monitoring procedures. Members and organization of the Program are shown in Appendix 1. The objectives of the Program are to:

1) characterize workplace TDI environmental concentrations based on use of standardized industrial hygiene monitoring and assessment procedures,

2) monitor employee health through medical surveillance questionnaires and spirometry, using approaches that help ensure maximal participation,

3) investigate potential cases of OA using a standardized medical monitoring process and evaluation of historical exposure experience,

4) create a registry of OA cases, if any, occurring among workers with potential exposure to TDI in the production environment,

5) evaluate the effectiveness of the Program methods, including the standardized health and environmental monitoring procedures, and

6) communicate the Program findings to study subjects, plant management, and the scientific community in a manner consistent with Centers for Disease Control and Prevention (CDC) and ACC guidelines for assuring the quality, objectivity, utility, and integrity of the information presented.

B. Review of Existing Information

TDI is a highly reactive monomer that has long been recognized as a respiratory tract irritant capable of causing asthma-like reactions in humans at high concentrations (Fuchs and Valade, 1951). Numerous studies carried out since the 1950s in TDI producing and using facilities have led to a better understanding of the respiratory effects of TDI exposure. These range from self-limited irritant effects to chronic effects such as induction of bronchial asthma and possibly an accelerated loss of pulmonary function.

Distinguishing between transient irritant effects and effects secondary to a state of hyperresponsiveness induced by TDI exposure can be exceedingly important in terms of consequences to the affected employee. If the response is due to a direct irritant effect, the employee should be able to return to work in the same job upon cessation of symptoms. However, if the employee has developed respiratory hyperresponsiveness due to a single massive or repeated lower-level exposure, continued exposure may lead to asthma, an exacerbation of symptoms, and/or the development of chronic rhinitis. Under such circumstances, further contact with TDI should be avoided. As many studies have shown, continued exposure can lead to increasingly persistent and severe respiratory symptoms (Paggiaro et al., 1984; Rosenberg et al., 1987; Pisati et al., 1993; Tarlo et al., 1997). Additionally, the duration of symptomatic exposure, measured in months and years, is an important correlate of the persistence of asthmatic symptoms even after complete removal from further exposure. Thus, early

detection of respiratory sensitization to TDI is very important in limiting any long-term health consequences to the employee.

In addition to distinguishing between transient irritant effects and a state of specific bronchial hyperresponsiveness to TDI, exposure to other work and non-work-related factors such as cigarette smoke, common environmental allergens, or infectious agents may complicate assessing the etiology of respiratory symptoms. In a recent longitudinal study of over 600 apprentices in animal-health technology, pastry making, and dental hygiene, medical monitoring included yearly skin prick tests to both work-related allergens (e.g., animal antigens, flour, and latex) and common environmental antigens (Nguyen et al., 2003). During the surveillance period, approximately equal numbers of subjects developed positive prick tests to common versus occupational allergens. Approximately 25% of the subjects who developed positive responses reacted to both occupational and common allergen challenges, and the majority of these subjects converted to positive responses during the same examination cycle. These findings further complicate the interpretation of respiratory symptoms as being due to occupational versus non-occupational exposures.

With respect to estimating the incidence of specific health outcomes such as new onset OA in a population, longitudinal studies are generally regarded as superior to other types of studies. A recent critical review of longitudinal TDI studies revealed a clear downward trend in the annual incidence of TDI-induced asthma that correlated with decreases in environmental TDI concentrations (Ott et al., 2003). The available data covered a period from the 1950s through the mid-1990s. In the studied work populations, incidence rates of new onset OA due to TDI have declined to less than one per 100 employees per year. Assuming that comparable definitions and work-up of TDI-induced asthma cases are utilized in the present Program, a population of 300 employees followed over a five-year period should yield no more than 21 cases with 95% confidence, provided the underlying annual incidence of new onset OA is one per 100 employees or less.

Asthma was defined in a recent Expert Review Report (NHLBI, 1997) as a chronic inflammatory disorder of the airways involving interactions of many cells (including mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils, and epithelial cells) and cellular elements. Symptoms associated with recurrent asthma episodes may include wheezing, breathlessness, chest tightness, and coughing, and these episodes may be accompanied by airflow limitation that is at least partly reversible spontaneously or with treatment.

OA has been described as a “disease characterized by variable airflow limitation and/or airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace” (Bernstein et al., 1993). OA cases may be further subdivided into those with no apparent latency period (often arising as a result of single exposures to highly irritating vapors) and those with a latent period (cases for which an IgE- or cell-mediated mechanism has been identified or for which the mechanism is unknown).

TDI-induced asthma can be characterized as a condition of bronchial inflammation and hyperresponsiveness induced by TDI exposure and manifesting itself as transient symptomatic narrowing of the bronchi upon subsequent exposure to low TDI concentrations (e.g., 1 to <20 ppb for up to 30 minutes)(Ott et al., 2003). The severity of symptoms, the timing of reactions subsequent to exposure (immediate, late, dual, and atypical), and the challenge dose initiating a response may be

quite variable. Furthermore, Malo and colleagues have shown that single day challenge protocols may fail to detect responses in some individuals with diisocyanate asthma (Malo et al., 1999).

Histological studies of subjects with TDI-induced asthma have revealed similar findings to those seen among patients with non-OA, including bronchial mucosa exhibiting inflammatory cell infiltrate, thickening of the reticular basement membrane, and widening of the intercellular spaces between basal epithelial cells (Saetta et al., 1992).

Clinical assessment based on medical history alone can often result in an erroneous diagnosis of OA. For example, Malo reported that symptom histories did not discriminate well between persons with and without OA in a large series of referrals (Malo et al., 1991). In two other series of suspect cases, only 30-41% of the referrals could be confirmed as having OA by specific TDI challenge (Baur et al., 1998; Moscato et al., 1991). Inhalation challenge testing is not readily available as a confirmatory OA test in the U.S.; thus other objective measures will be needed for the present study. In a recent review of methods useful in diagnosing diisocyanate asthma, Bernstein and Jolly (1999) stressed the importance of serial measurements of lung function in relation to exposure. This approach could be particularly informative where there is co-ordination of personal air monitoring with the serial lung function measurements.

Regional and national OA surveillance systems have been instituted in a number of countries, mostly since the mid-1980s with the exception of the Finnish reporting system, which dates to 1974 (Meredith and Nordman, 1996). The data provided by these programs have been helpful in gauging overall OA trends and trends with respect to specific classes of causal agents and industry. However, case definitions of occupational or work-related asthma have varied widely from country to country, and case finding generally relies on reports of medical professionals supplemented by other data sources such as compensation claims and workplace inspections. There may be underreporting of cases because the relationship of symptoms to work was not investigated or because of a lack of objective evidence such as variable airflow limitation related to exposure (Klees et al., 1990; Jajosky et al., 1999; Henneberger et al., 1999). There may also be over-reporting due to misdiagnosis or incorrect identification of causative agents. Some systems such as the NIOSH Sentinel Event Notification System for Occupational Risks (SENSOR) define work-related asthma as encompassing work-related aggravation of pre-existing asthma as well as new onset OA (Jajosky et al., 1999). At least two reporting systems, those of Finland and Quebec, routinely include inhalation challenge testing in the case validation process and hence provide superior documentation both in terms of the OA diagnosis and in identification of the causal agent. In both settings, clear downward trends have been observed in the yearly rates of new OA cases attributable to all diisocyanates combined (Meredith and Nordman, 1996; Malo et al., 2001).

There is also evidence of declining trends, particularly during the 1990s, in reported diisocyanate-related OA cases in the U.S., U.K., and Canada (Ross et al., 1995; Meyer et al., 1999; McDonald et al., 2000; Malo et al., 2001; Tarlo and Liss, 2002; NIOSH, 1994; NIOSH, 1999; NIOSH 2002). In the U.S. SENSOR data, the proportion of cases of work-related asthma reported as due to diisocyanates declined from 19.4% in 1988-1992 to 15.5% in 1993-1999 [based on two states, Michigan and New Jersey] (NIOSH, 1994; NIOSH 2002). For the two states added to the SENSOR Program in 1993 [California and Massachusetts], the proportion of work-related asthma cases reported to be due to diisocyanates was 3.0% during 1993-1999 (NIOSH, 2002). With respect to TDI, there was a decline in

reported OA cases from 13.7 per year in 1993-95 to 6.0 per year in 1996-1999 based on all four reporting states (NIOSH, 1999; NIOSH 2002).

As noted above, studies of OA outcome after removal from further exposure have generally concluded that shorter duration of symptomatic exposure is associated with a better prognosis after cessation of exposure. In Ontario, Canada, where a requirement for environmental and medical monitoring of workplaces using diisocyanates was legislated in 1983, it appears that early diagnosis of OA has resulted in a better outcome as reflected in favorable hospitalization statistics and improved pulmonary function parameters in recent years (Tarlo et al., 2002).

Several studies, including two undertaken in TDI production environments, have provided data suggesting that induction of respiratory sensitization might be caused by non-routine peak exposure incidents involving exposure to diisocyanate concentrations well above 20 ppb (Weill et al., 1981; Bugler et al., 1991; Bernstein et al., 1993; Ott et al., 2000). This remains an open question in part because few studies have incorporated collection and analysis of real-time industrial hygiene measurements or tracking of acute overexposure episodes (Baur et al., 1998b; Ott et al., 2003).

C. Specific Aims and Hypotheses

This pilot study seeks to enroll all employees with potential TDI exposure at all North American TDI production facilities in a structured program of medical and environmental monitoring over a five year period. Representatives of five companies comprising six plants with approximately 300 employees participated in the initial project planning. Within the last year, two of these TDI production plants have closed, and there has been a consequent decline in the expected number of participating employees. Because many of the specific aims of the project are descriptive in character, and in light of the developmental nature of the project, it was felt worthwhile to proceed, acknowledging that it may not be possible to fully achieve all of the Specific Aims listed below due to the reduction in the universe of potential participants. If the current pilot data collection protocol is successful, the experience gained in this project should permit application of the methods to the much larger population of workplaces in which diisocyanates are used in the production consumer goods such as foams, plastics, adhesives, and paints.

Sample Size

This pilot study consists of all US TDI Plants. Although the total number of participants is small, this pilot project contains the entire population of US TDI workers.

Medical Surveillance

Aim 1. Define a practical, science-based model program for medical monitoring of employees working with diisocyanates and evaluate the operating characteristics (sensitivity and specificity) of various components of the program in identifying cases consistent with work-aggravated, work-related, and TDI-induced asthma.

Hypothesis 1. A program of scheduled medical monitoring in the TDI manufacturing environment can feasibly achieve 75% participation of eligible employees and 75% detection of individuals who are subsequently classified as consistent with work-aggravated, work-related, and TDI-induced asthma. This program will subject no more than twice the number of employees to a Stage II protocol work-up than are categorized as consistent with TDI-induced asthma based on completing the Stage II and Stage III work-ups.

Measurement of Hypothesis 1. In determining participation rates (the ratio of participating to eligible employees), the denominator will be the total number of persons judged eligible for the Program. Eligibility is defined under Section II.A.1 Enrollment of Participants. Two different measures of participation will be examined. Initial participation will be judged by completion of the enrollment forms plus the Intake Questionnaire and spirometry testing. Full participation will be judged based on having completed a Periodic Questionnaire either within six months of the ending date of the study or up to six months after the date of withdrawal due to leaving the TDI work area. In addition, full participation would mean the employee had participated in the staged protocol if requested to do so. Observed participation rates will be compared to those hypothesized above.

The percent detection of employees with work-aggravated, work-related, and TDI-induced asthma as specified per the staged medical protocol (see Medical Monitoring Flow Chart [Appendices 2-8] and outcome categories designated in the form: Work-up Classification: Completed by Consulting Pulmonologist [Appendix 9]) is measured as the ratio of work-aggravated, work-related, and TDI-induced asthma cases identified among employees referred to Stage II (see Appendices 5 & 6) of the medical monitoring protocol (based on the scheduled monitoring program) divided by the total number of incident cases (includes cases identified through the scheduled medical monitoring program, through direct consultation with an occupational physician, through worker's compensation records and through outside physician referral). The available documentation for all suspect cases will be provided to the external pulmonary consultant for assessment. The percent detection will be compared to the hypothesized value. Additionally, the percent yield of cases among employees referred to the Stage II (see Appendices 5 & 6) work-up and who participated in the Stage III (see Appendix 7) evaluation will be calculated and compared to the yield hypothesized above.

As defined in this protocol, work-aggravated and TDI-induced asthma are subcategories within the broader category of work-related asthma. (See Work-up Classification: Completed by Consulting Pulmonologist, Appendix 9)

Aim 2. Assess the effectiveness of specific methods (e.g., questionnaire items, spirometry) and procedures (e.g., frequency, timing) of medical monitoring programs, using screening and follow-up data obtained during medical surveillance of TDI-production employees.

Hypothesis 2. A series of questionnaire items can offer satisfactory operating characteristics (i.e., a positive predictive value of 50%) as a screening tool in detecting asthma that is confirmed on clinical follow-up, among individuals working in the TDI-production environment.

Measurement of Hypothesis 2. The responses to the four asthma symptom questions on the Intake (Appendix 10), Periodic (Appendix 11), and Second-tier Questionnaires (Appendix 12) will be examined in relation to asthma outcome as specified under Section II. C. Medical Assessment of

Asthma. Analyses will be performed to determine which combinations of questions best predict meeting the asthma definition. Results will be characterized in terms of the positive predictive value of these questions.

Aim 3. Determine to what extent utilization of a standardized medical monitoring program facilitates early detection of TDI-induced asthma cases (reduced duration of symptomatic exposure) and leads to a favorable outcome after cessation of exposure.

Hypothesis 3. Implementation of the Program will result in no more than six months of symptomatic exposure for any case of TDI-induced asthma and a complete cessation of asthma-related findings within one year of case detection.

Measurement of Hypothesis 3. We will measure the interval (in months) between the date symptoms were first reported (as identified in the Intake [Appendix 10], Periodic [Appendix 11], or Second-tier Questionnaire [Appendix 12] or the TDI clinical encounter form [Appendix 13]) and the date of medical removal from the TDI work environment due to findings consistent with a diagnosis of TDI-induced asthma. The distribution of symptomatic exposure intervals and the mean symptomatic exposure interval will be computed and compared to the hypothesized value and historic values for duration of symptomatic exposure in other settings. All employees having a diagnosis of TDI-induced asthma will be re-tested at one year after the prior removal date using the symptom questionnaires (and including assessment of current use of asthma medications), spirometry, and the same test series that was used to initially assess variable airway limitation. Analyses, as specified under Section II.E.: Methods of Statistical Analysis, will examine the relative change in each endpoint during the course of the year.

Epidemiological

Aim 4. Determine as accurately as possible the annual incidence of cases consistent with TDI-induced asthma in the TDI production environments that are compliant with current occupational exposure limits and accepted industrial hygiene practice.

Hypothesis 4. The annual incidence of TDI-induced asthma in the TDI production environment is well under 1% provided TDI concentrations are maintained below proposed recommendations by the American Conference of Governmental Industrial Hygienists (ACGIH) and a rigorous clinical work-up of potential cases is accomplished.

Measurement of Hypothesis 4. The outcome of interest, a determination of findings consistent with a diagnosis of TDI-induced asthma, will be assessed based on the staged medical monitoring protocol (see Medical Monitoring Flow Chart, Appendices 2-8) designed to identify subjects with asthma findings and then to assess work-relatedness and specific TDI-relatedness of the findings. Because distinguishing between asthma that is coincidental to or aggravated by factors at work versus being induced by work-related factors can be difficult and because some individuals may withdraw from the study before such a determination can be made, it is possible that a portion of the indeterminate asthma cases are TDI-induced. In the analyses this issue will be addressed by computing an average annual TDI-induced asthma rate both including and excluding the indeterminate asthma cases. The denominator for the rate calculation will be person-years at risk. In addition, TDI measurement data

will be analyzed in relation to the existing ACGIH recommendations for TDI to determine if ACGIH guidelines had been exceeded in any similar exposure group (SEG) after adjustment for respirator protection if appropriate. Analyses will be performed separately for any SEGs with measured TDI concentrations (time-weighted average (TWA) or Short-Term Exposure Limit (STEL)) exceeding ACGIH guidelines.

Aim 5. Assess the likelihood that work-related asthma occurrences in the TDI manufacturing environment are associated with non-routine exposures to TDI or other agents.

Hypothesis 5. In the TDI production environment with an active event reporting system and industrial hygiene program, the majority of work-related asthma cases will be associated with non-routine exposure episodes.

Measurement of Hypothesis 5. As previously, the outcomes of interest are a determination of clinical findings consistent with work-related asthma and the subcategories of work-aggravated and TDI-induced asthma as specified in the form entitled: Work-up Classification: Completed by Consulting Pulmonologist, Appendix 9. Non-routine exposure episodes will be identified through a compilation of Acute Inhalation Worksheets, Appendix 14, indicating the occurrence of such exposure incidents and the severity of symptoms associated with those incidents. Analyses will be conducted to determine the percentage of work-related asthma, and the subcategories of work-aggravated and TDI-induced asthma, cases associated with prior acute inhalation episodes. The specific analysis approach is discussed under Study Design: Methods of Statistical Analysis.

Aim 6. Assess the effectiveness of industrial hygiene, medical surveillance, and early removal of sensitized employees from subsequent TDI exposure in preserving long-term pulmonary health.

Hypothesis 6. Effective protection of lung health is afforded TDI production employees by control of workplace exposures, medical surveillance, and early removal of sensitized employees. Key lung function parameters (forced vital capacity [FVC] and forced expiratory volume at one second [FEV1]) will show no greater rate of annual decline than that observed for comparable members of the U.S. general population.

Measurement of Hypothesis 6. Spirometry will be measured annually as specified in the Study Design Section of this protocol under Medical Monitoring Process. We will specifically measure FVC and FEV1 and will analyze findings separately among employees without asthma, employees with a previous history of asthma or with current work-related and non-work-related asthma, and employees who are determined to have TDI-induced asthma. Specific measures will be FVC and FEV1 at entrance to study and rate of change in these parameters over time. Standard analysis procedures, as specified in Study Design: Methods of Statistical Analysis will be used to analyze these data on a cross-sectional basis at entrance to study and then longitudinally as sequential data become available. Potential confounders to be controlled for in these analyses are gender, age, height, weight, ethnicity, cigarette smoking, and change in weight. The analyses will examine the potential effects of work exposures, namely full-shift TWA estimates by SEG, frequency of high potential exposure tasks (HPET), and prior acute inhalation exposures in relation to FVC and FEV1 and will test for effect modification by age, gender, and cigarette smoking. Comparisons of annual rate of decline in FVC and FEV1 will be to our internal study comparison groups and other published population data.

D. Implementation Plan

1. Responsibilities

After conducting preliminary discussions in 2001, the ACC Diisocyanates Panel and NIOSH formalized a research and development collaborative program (Program) through a memorandum of understanding (MOU). This Implementation Plan provides guidance on implementing the MOU and references the preliminary work, where appropriate, to help the Program continue from its earlier activity. If any aspect of this protocol appears to be in conflict with the MOU, the MOU is considered to govern. However, any deviation from the project protocol required to comply with the MOU must be approved by the NIOSH HSRB and The Dow Chemical Company IRB before implementation.

Lee Petsonk, MD is the NIOSH principal investigator and responsible for all NIOSH data management and analysis functions. However, at each facility, responsibility for the project protocol lies with the company medical director (BASF, Bayer) or plant physician (The Dow Chemical Company). For the ACC, responsibility for the project is the diisocyanate panel manager, Sarah McLallen.

The organization of the Program is described in the MOU. The Program comprises a management group and four task groups. The management group, the Integration and Communication Group (ICG), oversees the work of the four task groups, 1) the Data Analysis Task Group (DATG), 2) the Exposure Assessment Task Group (EATG), 3) the Medical Surveillance Task Group (MSTG), and 4) the Data Management Task Group (DMTG), as discussed in section 6 of the MOU. Appendix 1 shows the Program organization chart and includes participants in the preliminary collaborative work.

The NIOSH and The Dow Chemical Company Human Studies Review Boards (HSRB) will provide ethical review of the protocol to assure 1) the health and safety of study subjects, 2) the maintenance of confidentiality of the data, and 3) the timely communication of results to study subjects and the scientific community.

As provided in the MOU, a Scientific Peer Review Panel will also be formed to maximize merit, feasibility and productivity of the proposed protocol. The ICG may also use other mechanisms to provide scientific review and to assure that the aims of the protocol are reflected in the final report.

Prior to or during the first year of the study, NIOSH will visit each site and assist with training on the spirometry, the exposure sampling methods, and the sampling strategy. NIOSH will also assist with sampling at each site subject to need and availability. In subsequent years, as needed, NIOSH personnel will visit each site to answer questions, ensure consistency of data collection, and assist with sampling. If additional resources are needed at a site, NIOSH will consider providing support on a case-by case basis.

2. Schedule and Timelines

When does the study start?

The study will start within three months after the protocol has been approved by the Human Studies Review Boards but not before training has been completed at each site on the use of data collection instruments. We anticipate a study start date of October 31, 2006 given current progress.

When does the study end?

Assuming a October 31, 2006 start date, the study data collection will end on October 31, 2011. However, medical protocols and follow-ups will continue beyond that date, until completion as specified in the protocol.

When do we anticipate reports/documents?

A yearly progress report will be issued January 15 each year after the study start. This progress report will report the number of persons in the study, the number of data instruments completed, the number of spirometry tests performed, the number of consultations with the pulmonary expert, and the number asthma cases by type suspected and/or confirmed. The final report will provide an overall project summary and description of analyses of all hypotheses, may include one or more manuscripts submitted for publication in peer review literature, and will be completed by October 31, 2012. Other reports will be submitted as required by law.

When will we communicate to study subjects?

Each participant will receive a timely report (e.g., within 30 days of testing) of their personal medical findings generated by company medical personnel. Participating facilities will use existing processes for communication of all surveillance and other study-related results. Medical test results will be communicated as required by The Dow Human Studies Review Board either personally and documented in the employee's medical record or in writing.

There will be yearly communication on study progress to study participants after completion of the yearly progress report. Final study results will also be communicated to subjects within 60 days of completion of the final report. Should clear adverse effects be observed before study completion, study participants will be informed of these findings as soon as practical.

II. Study Design

This section of the study protocol describes the determination of eligibility for participation in the Medical Surveillance Program, the period of recruitment into the Program, the specific methods to be used in collecting exposure and health-related data for participants, procedures for documenting early withdrawal of participants, methods of statistical analyses to address the aims and hypotheses of the Program, and the rationale for interpretation of the results of the Program.

Given that there are several unknowns such as asthma incidence and exposure levels in this study and since new instruments are being designed for data collection, we will periodically review the protocol to determine if there are any changes needed to improve the design or the collection of the data. A protocol addendum will be written to describe any material changes in the protocol procedures and reviewed by the ICG and approved by the Institutional Review Boards.

A. Enrollment of Participants

1. Eligibility criteria

a. Study group

The study volunteers will be recruited from TDI plants at BASF in Geismar, Bayer in Baytown and New Martinsville, and The Dow Chemical Company in Freeport. We estimate that during the study period, there may be up to 300 eligible workers with potential TDI exposure at these sites combined.

All workers performing job tasks that require them to work in areas of potential exposure to TDI will be asked to participate in the study. The study site coordinator will fill out the Registration Form (Appendix 16) for all eligible workers. Inclusion in the study group will be based on 1) the expectation that qualifying individuals will be performing job tasks that may be anticipated to require them to work in areas of potential exposure to TDI during any given year, 2) a reasonable expectation of being able to participate fully in the on-site Medical Surveillance Program as described in this protocol (to elaborate, short term employees, whether contract or directly employed, will not be eligible as they do not participate fully in the on-site Medical Surveillance Program. Long term employees who are under contract will be eligible to participate if they participate in the on-site Surveillance Program but ineligible if they don't.), and 3) signing the consent to participate form (Appendix 18). Workers who report to the clinic with symptom of a TDI exposure or workers who are exposed during a TDI incident will be asked to participate in the study if they are not currently in the study. Cases arising among individuals who experienced an incident but were not originally enrolled in the study will be described in the project reports, but will be included as incident cases only if the individuals were initially eligible to participate in the cohort. Workers who initially decline to participate can begin participation by signing the consent form at any time. A vendor will be responsible for organizing the database for the study (See Study Conduct, Data Storage and Handling, sections 3 and 4). This vendor will provide lists of all registered eligible workers for each participating plant.

Job tasks with potential or known exposure to TDI include production-, maintenance-, storage- and transportation-related tasks, housekeeping/incident response and laboratory analysis of TDI process samples. To be eligible, a worker should be anticipated to perform tasks requiring their presence in areas of potential TDI exposure averaging over ten hours per week throughout the year or to perform job tasks with a high potential for direct contact with TDI averaging at least 24 times per year. More than one task with potential TDI exposure may be counted during a single shift. Any employee who has experienced a TDI incident exposure situation is also eligible. Individuals will remain eligible for inclusion in the study group even if they had previously worked with other diisocyanates or had concurrent exposures to other diisocyanates. The responsibility for assessing eligibility will rest primarily with site industrial hygiene and human resources personnel utilizing the guidance provided in this protocol. Extenuating circumstances that would preclude any otherwise eligible worker from participating in the Medical Surveillance Program should be documented on the Registration Form (Appendix 16) to be included in the Program record, with the reasons for the exclusion.

At any time, study participants may choose to terminate their involvement in the study. If this occurs, they will be asked to complete a brief form that addresses the reason for termination (Appendix 19) and asked to complete a Periodic Questionnaire (Appendix 11). Study group members who have been transferred out of the TDI unit, but remain at the same company location, will be asked to continue in

the study even though they may no longer have potential for TDI exposure. This continuation will be true regardless of the reason for transfer.

b. Comparison group

Comparison groups in this study will be taken from published results of other populations. No internal comparison group will be used in this study. However, if participating sites determine in advance that they are able to identify a suitable comparison group, they can at their option propose an addendum to this protocol to offer the same medical surveillance program to such employees. If an appropriate comparison group is identified, both The Dow IRB and NIOSH HSRB approvals will be requested before including those individuals in the study.

c. Recruitment period

Study participants will be recruited for a period of two years, beginning after Human Studies Review Boards approval and at the designated study start date. The study will run for 5 years. However, the recruitment period could be lengthened based on the recommendation of the ICG that an insufficient number of participants have been recruited for the study. A sufficient number of participants are difficult to define given the unknown prevalence of TDI-induced asthma in these workers. Nevertheless, the ICG will determine if the recruitment period should be lengthened based upon power calculations for finding statistically significant effects using the rates of TDI-induced asthma observed after the first two years of recruitment. The power calculations will select a number of participants to be able to detect a doubling of risk using an α of 0.05 and β of 0.50.

Employees who agree to participate will complete a Participation Election Form and sign a Consent Form as shown in Appendix 17 and 18 respectively. Employees who decline participation will be asked to indicate that they decline to participate on the Participant Election form. Medical staff will fill out the declination information on non-participants.

Each participating plant site will submit a registration form (Appendix 16), with assigned SEGs, to the data management contractor for all eligible employees (as defined in eligibility criteria) and a rationale for categorizing them as eligible. All eligible employees will be informed about the study aims and procedures, given opportunity to ask questions, and encouraged to participate. Employees who agree to participate will sign a consent form and this will be indicated on the Registration form. Employees who decline participation will be asked to sign a declination and provide certain information. In order to compare participants to non-participants, this form will ask non-participants for information on their gender, age, ethnicity, type of work, tenure, and whether they are a contract worker.

The recruitment process will be adapted to the specific needs of each plant site but will be agreed to by company management, TDI unit management, plant medical personnel, and NIOSH staff. Each plant site may have its own specific needs. Settings for this recruitment process include, but are not limited to the following options:

- Oral presentation (see Appendix 38) during scheduled safety meetings (all shifts) or other forum as preferred by the plant. This would be the preferred method of interaction with employees but may not be feasible at all sites.

- Distribution of printed material outlining the study aims and procedures and participation forms; staff would be available to answer questions on a case-by-case basis. (see Appendix 38)

- Eligible employees may report to the medical department and be briefed on the study aims and procedures, and complete participation forms.

- Employees reporting acute inhalation episodes will be informed of the study, given an informed consent and provided an opportunity to ask questions to the Medical Department. They will be provided information on the study aims and procedures and asked to sign the participation or the declination forms.

  During the first two years of the study each plant medical department will be provided an updated list of all eligible study participants at their site including contractors. Whenever feasible, they will ask all non-participants to reconsider and volunteer to participate in this study. Forms will then be offered as a participant or non-participant, as outlined above.

2. Collection of baseline information

Once participants are identified and registration forms are completed, plant medical personnel will ask the employee to complete the Periodic Questionnaire as soon as possible and set up individual appointment times to complete the Intake Questionnaire, and baseline spirometry. All participants should complete their initial evaluation as soon as practical but definitively within six months of recruitment.

B. Exposure Assessment

Summary of exposure assessment:
A major objective of the exposure assessment portion of this study is to establish and implement a uniform strategy among all participating company sites that provides the exposure data needed to achieve study aims and hypotheses.

Exposure assessment needed to support the aims and hypotheses in this epidemiologic study will be accomplished in four ways. These include:

1. Quantitative exposure assessment (air sampling) of applicable TDI worker populations
2. Documentation of TDI potential exposure incidents
3. Documentation of potential exposure to agents other than TDI capable of respiratory effects
4. Retrospective Exposure Assessment

Quantitative Exposure Assessment

Quantitative exposure assessment will be done primarily using the Bayer Sampling and Analytical Method equivalent of the OSHA 42 method for measuring airborne personal exposures to TDI.

Quantitative TDI exposure assessment will involve collection of air samples representing shift length duration (TWA) Time Weighted Average exposure potentials as well as short term exposure of defined High Potential Exposure Tasks (HPETs), where the highest potential exists for TDI exposure.

Representative air monitoring of TDI worker populations at study sites will be accomplished by dividing workers into Similar Exposure Groups (SEGs). Dividing workers into SEGs groups them by (similar) exposure potential based on doing similar work tasks in basically similar ways. This facilitates the ability to characterize exposures for a population of workers based upon a sampling of exposures from a subset of workers in each group provided statistically significant sample numbers and random sampling are done. SEGs have been assigned for TWA and HPET exposure assessment in the study based on analysis of common tasks and jobs at participating company sites.

TDI Incident Exposure Documentation

Exposure potential affecting study objectives does not only come from quantitative sampling of workers performing routine tasks, but also from accidental exposures resulting from upset conditions, spills and releases to name a few. To capture exposure information primarily of a qualitative nature from these incidents an Acute TDI Inhalation Worksheet Form has been developed to document pertinent information on the potential exposure incident experienced by the worker. The form is intended to at least qualitatively characterize the incident circumstances, type of exposure, and the extent, severity and symptoms of exposure experienced by the worker(s) involved. Capture of this information capitalizes upon the fact that all participating company sites have extensive incident information documentation and investigation efforts to support this.

Reporting of Exposures to Agents other than TDI

Some level of characterization is needed for potential exposure to agents other than TDI that may have a potential confounding impact by causing respiratory effects to study population workers. To accomplish this an Agent Release Report Form was created to capture primarily qualitative information related to release incidents with potential exposure to agents other than TDI such as, but not limited to chemicals such as chlorine, phosgene, and HCl. Again, gathering this information capitalizes on well established incident information capture and investigation capabilities at participating sites.

Retrospective Exposure Assessment

The study is longitudinal from the study start date. However, if and when there is suspicion of occupational asthma in a study participant, a retrospective exposure review may be triggered. Site medical personnel would initiate the process by requesting data from site Industrial Hygiene. At this point the Industrial Hygienist will review past applicable exposures for the employee in question as well as history and results of incident investigations or other applicable records that may provide possible evidence of exposure.

All aspects of the study exposure assessment strategy are covered in detail on succeeding pages.

1. Industrial hygiene monitoring program

The Industrial Hygienist monitoring program will be based on establishing SEGs and HPETs as defined in the IH Monitoring Data Collection Form shown in Appendix 20.

a. Sample collection and analytical methods

A TDI colorimetric badge will be the primary instrument used to determine personnel exposure assessment for Time Weighted Average (TWA), shift exposures. Operating instructions are given in Appendix 21. Validation studies are available that characterize the badge's response to a variety of factors, including temperature, humidity, sunlight, time, and interferences. As a result of this study's needs, a special optics reader has been designed for use to allow very low intensity color changes to be read. Tests conducted by the EATG show the limit of detection of the badge enabled by the Optical Reader to be approximately 3.0 ppb-hrs. The badge manufacturer, Morphhix, will provide quality control testing data prior to, and during the study.

The Limit of Detection (LOD) of the TDI colorimetric badge as determined in study work done by the EATG showed that the badge does not have the sensitivity to adequately characterize TDI exposure in short term exposure situations as represented by the High Potential Exposure Tasks (HPET) defined in this study. Therefore, personnel exposure assessment of defined HPETs will involve use of the Bayer CIHL Method 1.7.6, Determination of Airborne Isocyanates by Sampling on a 1-(2-pyridyl)piperazine-Coated Glass-Fiber Filter and Analysis by High Performance Liquid Chromatography (Appendix 32, Bayer Sampling and Analytical Method 1.7.6). This is OSHA Method 42 modified by coating the 37-mm glass-fiber filter with 2 mg of the derivatizing reagent, 1-(2-pyridyl)piperazine (PP), instead of the 0.1 mg quantity recommended in the OSHA method and loading the filter in the cassette with a stainless-steel back-up screen in place of the mixed-cellulose back-up pad. This fully validated sampling and analytical method is shown as Appendix 32.

b. Field validation of the Morphix, SafeAir TDI Badge

The field validation of the Morphix SafeAir TDI Badge provides the necessary quality assurance for its use in collection of TWA or shift duration personnel exposure data, comparing the badge to a modification of the OSHA-42 method as referenced in a. above. The validation will be done at one or more of the company sites prior to the start of the study. For details of the field validation, refer to Appendix 22, Field Validation of Morphix SafeAir TDI Badge.

c. Sample submission, processing and analysis when using the Bayer CIHL Method 1.7.6

The Bayer Material Science industrial hygiene laboratory in Pittsburgh, PA will provide unnumbered 37 mm glass fiber filter cassettes treated with PP for sampling HPET tasks. The Bayer lab will prepare and send them via overnight mail directly to those plants requesting them within two days. When the filters are received, they should be refrigerated until use. If the filters are not used within two weeks, they will be discarded.

Once the sampling is complete, the plant personnel will overnight mail the filters and supporting paperwork to the NIOSH Division of Respiratory Disease Studies, Surveillance Branch, in Morgantown, WV. The sample numbers provided by the TDI manufacturing plants will be logged and

new consecutive numbers assigned by NIOSH. The coding log will be maintained by NIOSH. The newly numbered cassettes will be sent by overnight mail to the Bayer lab for analysis.

Once the analysis is complete, Bayer will send the results electronically to the Surveillance Branch where the results will be matched to the paperwork from the plant and exposure levels calculated. The calculations and raw sample results will be sent electronically to the plant where the sample originated. The plants will be responsible for submitting the sample results to the contractor for entry into the data base.

The NIOSH lab in Cincinnati, OH will provide spiked samples (a minimum of 5% or at least one sample per analytical set) to the NIOSH Surveillance Branch in Morgantown. The spiked samples will be logged and sent by overnight mail to the Bayer lab for analysis for quality control purposes.

d. Other methods of assessing exposure

Occasionally another instrument may provide data in the absence of a badge reading. When it is determined this information correlates well to an actual exposure, it will be considered as part of the Acute TDI Inhalation Worksheet Form data. The instrument calibration and other factors will be assessed before incorporating this information into the employee record. One copy of all Acute TDI Inhalation Worksheets will reside in the employee medical record, with a second copy kept by the industrial hygienist site coordinator, and the third copy to the study data management contractor.

The Exposure Assessment Task Group discussed whether dispersion modeling would be valuable in estimating personnel exposure during events when employees were unprotected by personal protective equipment and were not wearing exposure assessment devices. One member gave evidence of a spill in a diked area where actual measurements downwind matched well with dispersion modeling data using a pool or lagoon model. This is not surprising since vapor concentrations would follow gas laws and variables such as meteorological data, distance downwind, and time spent in the area could be measured or estimated fairly accurately. It was agreed that this scenario could be modeled. Other scenarios, such as an employee being immediately downwind of a failed pump or line opening, would probably have far too much error to model. This situation would require an orifice size modeling methodology and becomes far more complicated when the desired output is to estimate exposure at a location downwind. However, if evidence is found that other modeling will work well for calculating an exposure estimate for a given situation, that method and calculation will be evaluated for use.

e. Training and Quality Control on Exposure Monitoring

NIOSH staff will train industry industrial hygiene personnel on the exposure data collection methods and procedures as resources are available. Refresher training will be performed when determined by NIOSH as needed, based on the results of ongoing quality assurance reporting, observation of procedures, and site-specific feedback. Refresher training will be conducted as feasible and within the resource limits. QC will include an initial visit to each plant, a second visit within 6 months, and periodic visits, as determined by NIOSH.

f. Retrospective exposure assessment

While the emphasis of this study is a longitudinal assessment of exposure from study start date, suspicion of occupational asthma on review of the Intake Questionnaire will trigger a retrospective exposure review. Plant medical personnel would initiate the process by requesting historical and current data from the industrial hygienist. The industrial hygienist will review the employee's current and past job classification and tasks. This review of the employee's work history would include monitoring data relevant to past exposures. Current monitoring data for the SEG will be forwarded to the requesting medical surveillance group. Root Cause Investigations and Incident Reporting Systems will be searched and applicable records provided to the medical group as possible evidence of exposure. Medical surveillance will be provided with a list of all previous work classifications (SEGs) and a list of high potential exposure tasks undertaken. The IH incident form will be the primary vehicle for communicating this information. Incident investigations will also be provided.

g. Reporting of exposures to agents other than TDI

All exposure incidents to other chemical agents at the facility will be captured on the Agent Release Report (Appendix 23). Because this study is focused on TDI, we will not attempt to measure air concentrations relative to other exposures. They will be characterized to the extent possible using available instrumentation and incident descriptions.

The TDI manufacturing process has the potential to expose workers to a variety of chemical substances, some capable of causing respiratory effects. All four facilities have incident reporting systems, which ensure the capture and documentation of these events. Documentation of the details of these incidents varies, depending upon the potential severity of the incident, outcome, and the number of persons affected. The individuals at the plant site responsible for completing the forms also have responsibility for reviewing incident reports to determine if an exposure affecting the outcome of the study should be captured in the Acute Inhalation Worksheet. Chemical exposure from agents within the TDI manufacturing complex may include, but is not limited to, chlorine, phosgene, hydrochloric acid, monochlorobenzene, dichlorobenzene, and carbon monoxide. Since many TDI production facilities are situated in larger manufacturing complexes, it is possible that exposure to other agents in the facility could also cause respiratory effects. All known chemical exposures occurring during working hours, regardless of source, will be investigated and characterized (contaminant, concentration if known, severity, etc.) either on the Agent Release Report or on the appropriate Medical Data Collection Form depending upon the nature of the event (chemical or biological) the event will either be captured on the Agent Release Report or appropriate Medical Data Collection Form. At the conclusion of the study, a complete list of all known potential confounding exposures will be included in the summary, along with their relationship to medical outcomes if known.

h. Monitoring of TDI

The following procedures will be used to monitor TDI levels in the workplaces:

1) Normal Operating Conditions: Scheduled

a) <u>TWA will be assessed as follows.</u>

i) If the SEG has fewer than six employees, all will be monitored quarterly.

ii) If the SEG has greater than or equal to six employees,

(1) At least six will be randomly chosen each quarter to be monitored, OR all will be monitored each quarter.
(2) The use of the random number generation feature in Excel or an equivalent method will be used to select employees to be monitored quarterly. If used, equivalent methods will be documented. Due to the variation in shifts among sites, NIOSH will assist each site in developing a sampling plan that minimizes the time the IH must spend in the field, yet achieves the goal of statistical validity and randomness.

iii) An exposure will be monitored once during each quarter on a randomly selected day during the quarter.
(1) Multiple persons from different SEGs can be monitored on the same day.
(2) If an SEG has more than one member, it would be helpful to monitor exposures from the members on at least two different days during the quarter. A member needs to be monitored only once during the quarter, but if there are several members, their exposures should be monitored on separate days when possible.

iv) Quarters are defined as follows:
(1) Q1: [Jan-Mar]
(2) Q2: [Apr-Jun]
(3) Q3: [Jul-Sep]
(4) Q4: [Oct-Dec]

v) Estimates of total variance (σ_T^2), variance within worker (σ_W^2), and variance between workers (σ_B^2) can be obtained.

vi) Stationarity will have to be assessed based on samples collected "before" and "after" turnaround as well as changes in exposures as plant "ages" respective to last turnaround.

vii) Autocorrelation should be minimized with this sampling scheme.

viii) Seasonality variation can be estimated.

ix) Arithmetic means can be estimated.

x) Geometric standard deviations can be estimated.

b) Task-Based Exposures for High Potential Exposure Tasks
i) These should be monitored using the same schedule as for TWA exposures. However, if the number of times the task is repeated during a year is fewer than 4, the worker should be monitored each time the HPET is performed. Workers should be randomly chosen when possible. If this is not possible, monitor the worker doing the task.

c) Each year the cumulative data will be assessed. If, based on an estimate of the 95th percentile relative to the ACGIH Threshold Limit Value (TLV) [TLV-STEL of 20 ppb for task-based, or ACGIH TLV -TWA [5 ppb]) using all samples collected during the study an SEG has:
i) greater than 5% excess of 0.5 x TLV, then repeat this sampling strategy for the affected SEG or HPET in the next year;
ii) otherwise, sampling will be performed in two quarters, randomly chosen for each SEG, the next year.

2) Turnaround

a) TWA will be assessed as follows.
i) If the SEG has fewer than six employees, all will be monitored during turnaround.
ii) If the SEG has greater than or equal to six employees, six will be randomly chosen to be monitored during the turnaround, OR all will be monitored. Be careful not to arbitrarily choose participants.

iii) To randomly pick employees from an SEG during a quarter, the procedure described in 1 (a)(i)(2)(b) above can be used.
iv) Assess TWA exposures for each participant on randomly selected days twice during the turnaround.

b) Task-Based High Potential Exposures
i) These will be monitored using the same schedule as for TWA exposures; however, if the number of times the task is repeated during the turnaround is fewer than 4, the worker should be monitored each time the HPET is performed; randomly choosing a worker may not be feasible. If not, monitor the worker doing the task

c) If the TWA and HPETs are monitored on a participant during the same shift, the TWA should be assessed with a single badge; the HPETs should be monitored with a single badge for each HPET.

3) Upset Conditions

a) TWA measurements will not be attempted.
b) Short Term Exposures. These should be monitored when determined to be feasible by the local personnel.
c) The Agent Release Report (Appendix 23) will be used to provide qualitative information about the potential exposure and is expected to be the primary source of exposure information.

4) Collection Times

a) For TWA exposure assessment, at least 90% of the time period should be monitored. For an 8 hour shift, the monitoring should be for at least 7.25 hours. If the shift extends beyond 8 hours, the full shift should be monitored using the 90% rule. The unmonitored time should not include tasks not represented in the monitored period.
b) For HPETs, the exposure distribution must be considered as the distribution of air concentrations all collected over a similar averaging time. Small differences in duration are unlikely to have substantial effect, but the shorter the task time, the greater the need to minimize the differences between the groups. In practice, the workers may not be available to change the monitor at a pre-specified period. So, sampling should begin as close to the actual beginning of potential exposure, and end as soon as feasible after the HPET is completed. The removal of potentially contaminated clothing should be considered part of the HPET.
c) Badges will be read within 24 hours.

c. Development of Similar Exposure Groups

SEGs as defined by the American Industrial Hygiene Association Exposure Assessment Strategy in its publication "A Strategy for Assessment and Managing Occupational Exposures", 2nd Edition, J.R. Mulhausen, J. Damiano, will be used to develop exposure estimates. If workers are assembled into groups reasonably anticipated to have similar exposures, exposure assessments of a few workers will be representative of the larger group. The size and complexity of the workplace, and the jobs and tasks conducted by the workers, dictate the quantity of the SEGs needed to characterize all workers' exposures.

The SEG concept was determined to be the best method of characterizing TDI exposure potential for the study. The SEG definition calls for grouping employees by similar exposure associated with performing similar tasks that present similar exposure potential. Exposure for employees within these

SEGs is believed to be similar as long as all employees in the defined SEGs perform a similar set of tasks involving TDI on a day-to-day basis.

After discussions, the following common SEGs were developed:

- TDI Loading/Shipping Personnel
- Drumming Personnel
- Field Unit Operators
- Process Chemist
- Engineers/Plant Supervision
- Laboratory Personnel
- Instrument Technicians
- Control Room Operators
- Shift Supervisors/Foremen
- Mechanical Maintenance for TDI

NIOSH industrial hygienists' visits to the participating company TDI Production facilities resulted in systematic discussion of TDI production process flow and the roles of the defined SEGs in the process. Discussion concluded that the defined common SEGs are adequate to characterize all potential TDI exposure in these operations. This list of SEGs represents all TDI tasks with the potential for exposure. These SEGs have been included on the IH Monitoring Data Collection Form shown as Appendix 20.

The use of these SEGs to partition exposure data will enable collection and analysis of exposure data in a uniform way across all participating sites. It is understood that exposure potential within each SEG can be unique to each site; however, tasks encompassing all of TDI production should fit within the confines of these SEGs.

Only one participating company facility, the Bayer New Martinsville facility, contains operations where TDI is a raw material in addition to a product. As a result, a set of SEGs that represents TDI use at this facility was developed and included on the IH Monitoring Data Collection Form. They are:

- TDI Use A Tech
- TDI Use B Tech
- TDI Use Maintenance
- TDI Use Engineers/Supervision
- TDI Use Tank Farm

SEGs will be used to categorize potential TDI exposures determined through air monitoring of routine operations and for categorization of TDI exposures as a result of TDI release incidents.

d. Development of High Potential Exposure Tasks

As discussed previously, there may be a connection between medical outcomes and peak exposure rather than TWA exposures to TDI. The High Potential Exposure Tasks (HPETs) attempt to characterize peak exposure. The application of HPETs in the context of TDI exposure may occur during the normal or routine course of TDI production or during emergencies involving release of TDI.

HPETs represent tasks that present a high potential for TDI exposure primarily due to handling of TDI outside the normal containment of totally enclosed processes.

The HPETs below are a list of tasks common to all participating company TDI production processes. The list was refined and confirmed during meetings with the NIOSH Industrial Hygienists at participating sites, where systematic review of the flow of the production processes and HPET situations was conducted. This list determined the frequency of air sampling and categorization of incident exposure situations, where applicable.

- Equipment Drain/Decon
- Line Opening
- Process Sampling
- Waste Handling
- Hot Work
- Confined Space Work
- TDI Loading
- System Upset / Area Exposure
- Emergency Response

Once a year, each plant will submit an estimate of the annual frequency of each of these HPETs by SEG. The HPET Frequency form will be utilized for capturing this data. (See Appendix 24)

e. Use of personal protective equipment

The use of all personal protective equipment is captured on the IH Monitoring Data Collection Form, Appendix 22, as well as on the Acute TDI Inhalation Worksheet, Appendix 14. Since the study is focused upon respiratory health and the inhalation of TDI in the workplace, a summary of the protection afforded by the four facilities respirator programs is listed here.

When individuals perform tasks while wearing personal protective equipment, exposure monitoring will be conducted outside the equipment, but detailed annotation will be made as to the type of equipment the worker is wearing during the exposure monitoring. Also, any problems an employee may have which could reduce protection of the equipment such as fit, tears, high humidity, or breaking the seal during the tasks could trigger filling out the Acute TDI Inhalation Worksheet, if ambient TDI levels are significant. An overview of the policies used for personal protective equipment in general is shown in Appendix 30.

2. Linking measurement data to employees

a. Job-exposure matrix

A job-exposure matrix assigns each worker an exposure estimate for each day worked. The SEGs and HPETs will be used to relate group exposures to individual work assignments. The plant study coordinator will indicate the SEG for each eligible worker in the registration process. Participants will be asked about changes in their SEG annually. A question about job change and new SEG is included on the Periodic Questionnaire. The job changes will be recorded at the yearly medical examination.

TWA TDI measurements and HPET measurements will be the only routine exposure linked to the SEG, but other incident exposures will be taken into consideration on the incident form as described below.

b. Assessment of full-shift TWA TDI concentrations

Full-shift TDI concentrations will be estimated for each of the 15 SEGs listed on the IH Monitoring Data Collection Form using observations provided on those forms and incorporated into the study database. Only sampling data designated as having a TWA weighting period and being classified with respect to SEG will be utilized in this assessment. Individual TDI concentrations will be calculated as the badge reading in ppb-hrs divided by the duration of sampling expressed in hours (hrs) or minutes and expressed as a TDI concentration (ppb). Sample results less than the limit of detection will be assigned a value of one-half the limit of detection for the sampled period. In job task situations where a respirator was used, the type of respirator used will be captured and documented along with the exposure results on the IH Monitoring Data Collection Form. This will enable adjustment of exposure concentrations to account for respirator use if so decided as the study progresses. If this is done, a protection factor will be pre-assigned for each of the four respirator designations specified on the IH Monitoring Data Collection Form. Literature references supporting the chosen factors will be incorporated into the study documentation.

Frequency plots of the TWA estimates (or box whisker plots) will be constructed yearly by site for each SEG to characterize the distributions in terms of shape and to estimate mean TDI concentrations on a percentile basis (e.g., estimated TDI concentration for the 50^{th}, 75^{th}, 90^{th}, and 95^{th} percentile). According to the IH sampling plan, there will be up to approximately 24 measurements per SEG per site per year. Similarly, results will be aggregated across years to characterize the distribution by SEG and site, across sites to characterize the distribution by SEG and year, and across SEGs to characterize the distributions by site and year. These plots will be helpful in identifying patterns of results that warrant further scrutiny.

Because the TDI concentrations may vary by SEG, site, and year, a Kruskal-Wallis test (analysis of variance comparing the ranks of the TDI concentrations across the 15 SEGs and four sites on a yearly and an aggregated basis) will be performed to determine if there are statistically significant differences in mean rank scores across these factors and to examine time trends stratified by SEG and site. If such tests yield statistically significant differences at the 0.05 level, Dunn's multiple comparison post-test will be used to identify combinations of SEGs or SEGs by site that can be grouped or should be kept distinct for summarization purposes. Groupings should be such that there is no more than a two-fold difference between the highest and lowest mean value within a grouping. Separate estimates of mean TDI concentrations will be then calculated for each distinct grouping and will be used in estimating mean TWA at any point in time for any SEG by site by year combination. These results will also be utilized for assigning mean TWA estimates and calculating ppb-years of TDI exposure for each participant.

c. Assessment of task-specific TDI concentrations

Task-specific TDI concentrations will be estimated for each of the nine HPETs listed on the IH Monitoring Data Collection Form using observations provided on those forms and incorporated into the study database. Sampling data, collected over the duration of the HPET weighting period and being classified with respect to HPET, will be utilized in this assessment. Individual TDI

concentrations will be calculated using the analytical results from the Bayer Industrial Hygiene Laboratory performing sample analysis and the volume of air collected in each sample as recommended by Bayer CIHL Method 1.7.6 to yield a TDI concentration in ppb. In job task situations where a respirator was used, the type of respirator used will be captured and documented along with the exposure results on the IH Monitoring Data Collection Form. This will enable adjustment of exposure concentrations to account for respirator use if so decided as the study progresses. If this is done, a protection factor will be pre-assigned for each of the four respirator designations specified on the IH Monitoring Data Collection Form. Literature references supporting the chosen factors will be incorporated into the study documentation.

Frequency plots (or box whisker plots) of individual TDI concentrations (both adjusted and unadjusted for respirator use) will be constructed yearly for each HPET and across all HPETs combined to characterize the distributions in terms of shape and to estimate TDI concentrations on a percentile basis (e.g., estimated TDI concentration for the 50^{th}, 75^{th}, 90^{th}, and 95^{th} percentile). Analysis will also include a comparison of duration of exposure with TDI concentrations for each HPET task.

Because the distributions of measured TDI concentrations may vary across HPET and over time, a Kruskal-Wallis test (analysis of variance comparing the ranks of the TDI concentrations across the nine HPETs on a yearly and cumulative basis) will be performed to determine if there are significant differences at the 0.05 level. Dunn's multiple comparison post-test will be used to identify combinations of HPETs that can be grouped or should be kept distinct for summarization purposes. Groupings should be such that there is no more than a two-fold difference between the highest and lowest mean value within a grouping. The TDI concentration distributions will then be characterized separately for these groupings.

Separately, the industrial hygienist contact for each participating site will provide, for every SEG, estimates of the expected yearly frequency of performing each of the nine HPETs assuming a 260-day work year. This information will be utilized to link the mean yearly rate of HPET occurrences to individual study participants based on their SEG assignment history as captured on medical surveillance questionnaires.

Three measures reflecting relative intensity, cumulative frequency of performing high potential exposure tasks, and duration of HPET can be readily determined from the above data for each participant in the study. The first measure is the mean yearly rate of performing HPET tasks, which can be assigned to any individual for any point of time based on knowledge of the SEG to which that participant was assigned on that date. The second measure is the cumulative frequency of HPETs, which is calculated by multiplying the mean yearly rate of performing HPET tasks by the years of work summed across all jobs held. The duration of HPET can be found on the industrial hygiene monitoring data collection form. If the distribution of measured TDI concentrations is shown to vary across HPETs, task time or over cumulative time, then these measures will be calculated separately for use in testing hypotheses 5 and 6.

It is very likely that these measures will correlate with the corresponding estimates of full-shift TDI TWA concentrations. Nieuwenhuijsen (1997) surmised that correlations regularly arise between peak and average exposure measures in the work place and provided examples of their concurrence in one

work setting. More specifically, in a TDI production environment, Ott et al. (2000) demonstrated positive correlations between full shift TDI TWA estimates and the frequency of routine HPETs using continuous paper-tape monitoring and also demonstrated correlations between these measures and the likelihood of being subject to acute exposure incidents. Because TDI exposure indices constructed using these three different measures are likely to be correlated (e.g., SEGs with higher mean full-shift TDI concentrations are likely to be those with more frequent HPETs and associated with acute exposure incidents), these exposure measures will be examined separately in regression models relating health outcomes to independent explanatory factors.

d. IH exposure incident reports

All potential exposure incidents will be investigated, and an Acute TDI Inhalation Worksheet (Appendix 14) or Agent Release Report (Appendix 24) will be completed. Incident occurrences will be accumulated in the data base and linked to participant, SEG, site, and year of event.

C. Medical Assessment of Asthma

1. Initial screening criteria

The medical monitoring process is defined by the sequential application of standardized examination tools following specified procedures as shown in Appendices 2-8. The Periodic Questionnaire (Appendix 11) will be administered immediately after registration, to determine if any participants should be entered directly into the staged medical protocol. Within six months from registration (ideally, as soon as possible), the Intake Questionnaire (Appendix 10) and spirometry will be completed by all participants.

a. On-going screening

The Periodic Questionnaire (Appendix 11) will be repeated after six months for employees new to their unit, and both spirometry and the Periodic Questionnaire will be completed by all on-going participants one year after initial assessment and each year thereafter.

b. Self-report of symptoms

In addition, employees enrolled in the study can visit the clinic to report symptoms consistent with asthma from a TDI exposure (Appendix 13, TDI Clinical Encounter Template). These symptoms will be recorded on the clinical encounter form, and further evaluation proceeds as discussed below.

2. Selection of candidates for detailed medical monitoring process

There are two ways a participant can proceed to the staged medical protocol to assess asthma. The first is the site physician or health professional judges that further clinical evaluation is needed because of safety and health concerns related to the potential development or presence of asthma. Second, participants are requested to complete the Second-tier Questionnaire, based upon responses in the Periodic Questionnaire. The participant is also referred to the staged medical protocol after meeting one of the specified criteria on the Second-tier Questionnaire followed by a physician or health professional assessment indicating the Staged Medical Protocol can be undertaken safely. The criteria that alert the site physician that the staged medical protocol is indicated are shown in the attached diagram entitled Medical Monitoring Flow Chart and associated footnotes (Appendices 2-8).

For participants indicating one or more of these criteria for referral to the Staged Medical Protocol, the site health professional reviews the responses to assure the participant understood the questions and responded appropriately.

Participants meeting one of more these criteria are then followed-up by the site physician using the TDI Clinical Encounter Form to document findings and rationale behind the clinical disposition.

3. Staged Medical Protocol

The Staged Medical Protocol is defined by the sequential application of standardized examination tools following specified procedures (see Medical Monitoring Flow Chart in Appendices 2-8).

a. Objective tests

Particular symptoms and/or findings recorded during these procedures trigger progression through a protocol-based evaluation of health status as shown in the Medical Monitoring Flow Chart. The data collected during application of the staged medical protocol and the forms used to assess this data are intended to permit classification of findings by the expert medical consultant. In addition, this data will assist the responsible clinician in medical diagnostic and management determinations.

Initial spirometry and the yearly follow-up spirometry will be carried out using NIOSH spirometers in accordance with the recommendations of the American Thoracic Society. (See Spirometry Procedures Manual [Appendix 25].)

The bronchodilator test and methacholine challenge as specified in the Medical Monitoring Flow Chart are presented in detail in the Appendices 27 and 28 respectively. Methacholine challenge is a standard test used to detect sensitivity to irritants or dust in the air and to diagnose asthma. A participant may experience a brief episode of coughing or chest tightness, which is reversed with a bronchodilator. Less frequently, they may experience headache, flushing, or sweating, which should last less than an hour. This test takes approximately 40 minutes, but may take longer depending on the sensitivity of the lungs. If necessary during the medical protocol to document improvement in sensitivity, this test may be performed a second time after two weeks away from potential TDI exposure.

When serial flow monitoring is performed, data will be entered into the OASYS © program, and the graphical and text output of that program will be returned to the appropriate medical department as well as stored in study files. For all participants who are requested to enter the staged medical protocol, a judgment by an expert consultant is recorded, after a review of all available data.

b. Clinical Assessment

The clinical interpretation of results of the medical evaluations for each participant is based entirely upon best medical judgment of the responsible provider and according to usual standards of care. Study participants with findings of potential interest will be evaluated further according to the Medical Monitoring Flow Chart. This chart provides clear guidance for determining when all available clinical data will be submitted to the consulting pulmonologist for evaluation and classification. Individual medical management, including treatment and restriction of exposures, will take into account project-related results, but is performed completely independently of any project activities.

4. External expert opinion

For each participant who is referred to the staged medical protocol, all results will be reviewed by the consulting pulmonologist for further clinical assessment. The consulting pulmonologist will provide an asthma classification (see below), after review of the available data. After the evaluation or consultant judgment, each participating employee can be assigned to one of the mutually-exclusive asthma/non-asthma definition categories as specified in the form: Work-up Classification: Completed by Consulting Pulmonologist. However, the clinical interpretation of results of the medical evaluations for each participant is based entirely upon best medical judgment of the responsible provider and according to usual standards of care.

The case classifications in relation to asthma that will be used in the analysis are taken from the Work-up Classification: To Be Completed by Consulting Pulmonologist (See Appendix 9). The classifications that will be assigned for the purposes of this study are:

1) Consistent with non-work-related asthma – Asthma caused by conditions not attributable to a particular working environment, nonspecific stimuli encountered both at and away from the workplace may trigger symptoms.
2) Indeterminate regarding work-related asthma – Asthma where workplace association is unknown or uncertain.
3) Consistent with work-related asthma – Asthma in which there is an association between symptoms and work causes and conditions attributable to a particular working environment and not to stimuli encountered outside the workplace.
   a) Consistent with work-aggravated asthma – Pre-existing or coincidental new onset asthma which is made worse (i.e., increased medication requirement, or important clinical worsening) by non-specific factors in the workplace.
   b) Consistent with TDI-induced asthma – Asthma caused by TDI in a working environment and not by factors outside the work environment.
   c) Consistent with Irritant-induced asthma/Reactive Airway Dysfunction Syndrome (RADS) -- Asthma caused by exposure to nonspecific irritants in the working environment and not by factors outside of the work environment
4) Consistent with asthma induced by other agent(s)

D. Termination of Surveillance/End of Study

Those persons who terminate employment, transfer to another location, or elect not to continue participation in the study, will be asked to complete a final Periodic Questionnaire at that time. The study will end five years after initial enrollment is completed. At the end of the study, all participants will be asked to complete a final Periodic Questionnaire if they have not done so within the past six months.

E. Methods of Statistical Analysis

Data analyses for this study will be conducted only on data sets that have been provided in accord with instructions from the ICG. These datasets will be locked versions of the study database. Both NIOSH and the ACC Diisocyanate Panel members will be provided identical copies of the datasets for analysis. Analyses will be performed using the Statistical Analysis System (SAS) version 8 for PCs,

unless otherwise specified. For each program run used to support analyses to be presented in output tables, a hard copy of the SAS program, the SAS log, and the SAS output will be retained for documentation and quality assurance purposes.

1. Selection of relevant variables

In this section, each relevant variable will be specified and labeled according to its source and use in addressing the six aims and hypotheses described previously.

Medical Surveillance (Aim 1 and Hypothesis 1)

This aim relates to defining a model program for medical monitoring of employees working with diisocyanates and evaluating the operating characteristics of various components of the program. The specific hypothesis corresponding to this aim relates to examining participation rates in the various components of the program. The following variables are needed to achieve this aim and test the hypothesis.

Data Element Description	**Source of data**	**Form of data**
Eligibility for Program	Eligibility Lists and demographic summaries provided by each site	Counts by site, age group (5-year intervals), gender, ethnicity (white, black, Hispanic, other), tenure, contract status, and job (according to SEG)
Agree to Participate	Registration form	Yes/No & Date
Participation in Intake Questionnaire	Intake Questionnaire (accepted form in database)	Yes/No & Date
Participation in Spirometry:	Intake Spirometry (accepted form in database)	Yes/No & Date
Age at Baseline	Intake Questionnaire	Computed from birth date and form date
Gender at Baseline	Intake Questionnaire	M/F
Ethnicity at Baseline	Intake Questionnaire	White/Black/Hispanic/Other
SEG at Baseline	Intake Questionnaire	As coded
Tenure	Intake Questionnaire	Years
Contract status	Registration Form	Yes/No & Date
Participation in Periodic Questionnaire	Periodic Questionnaire (accepted form in database)	Yes/No & Dates Administered
Participation Annual Spirometry	Accepted form in database	Yes/No & Dates Administered
Eligible for Stage I protocol	Medical monitoring – specified symptoms or findings	Yes/No & Date
Eligible for Stage II protocol	Medical monitoring – Finding of asthma	Yes/No & Date

Data Element Description	Source of data	Form of data
Evaluated at Stage III by Medical Consultant	Accepted form in Database	Yes/No & Date
Classification of consistent with TDI-induced asthma	Work-up Classification: Completed by Consulting Pulmonologist	Yes/No/Indeterminate & Date
Classification of consistent with work-aggravated asthma	Work-up Classification: Completed by Consulting Pulmonologist	Yes/No/Indeterminate & Date
Classification of consistent with work-related asthma	Work-up Classification: Completed by Consulting Pulmonologist	Yes/No/ Indeterminate + Date

Medical Surveillance (Aim 2 and Hypothesis 2)

This aim relates to assessing the effectiveness of this medical monitoring program in detecting asthma in the workplace. Specifically, the operating characteristics of a series of questionnaire items coupled with periodic spirometric testing together with the timing of testing will be evaluated. The specific hypothesis corresponding to this aim relates to the positive predictive value of the periodic screening tool in detecting asthma that is confirmed on clinical follow-up.

Data Element Description	Source of Data	Form of Data
Responses to each of 4 key questions	Periodic Questionnaire	Yes/No + Frequency of Occurrence + Date
Response to asthma question	Periodic Questionnaire	Yes/No + Date
FEV1	Annual Spirometry	Reading [x.xx] + Date
Consistent with asthma status	Consistent with asthma per Footnote 4 OR (Classification as C/W asthma by consultant pulmonologist)	Yes/No/ Indeterminate + Date

Medical Surveillance (Aim 3 and Hypothesis 3)

This aim relates to what extent utilization of a standardized medical monitoring program results in reduction in the duration of symptomatic exposure and leads to a favorable outcome after cessation of exposure. The specific hypothesis corresponding to this aim is that no case of TDI-induced asthma will have experienced more than six months of symptomatic exposure prior to removal from further exposure and there will be a complete cessation of asthma-related findings within one year of case detection.

Data Element Description	Source of Data	Form of Data

Data Element Description	Source of Data	Form of Data
Classification of consistent with TDI-induced asthma	Work-up Classification: Completed by Consulting Pulmonologist	Yes/No/ Indeterminate + Date
Classification of consistent with work-related asthma	Work-up Classification: Completed by Consulting Pulmonologist	Yes/No/ Indeterminate + Date
Symptoms onset date	Second-tier Questionnaire, Intake, or Periodic Questionnaire	earliest documented date
Responses to each of 4 key questions	Periodic Questionnaire at 1yr after TDI-induced Asthma Diagnosis.	Yes/No + Frequency of Occurrence + Date
Asthma medication use	Periodic Questionnaire at 1yr after TDI-induced Asthma Diagnosis.	Yes/No + Frequency of Occurrence + Date
FEV1	Annual Spirometry	Reading [x.xx] + Date
FVC	Annual Spirometry	Reading [x.xx] + Date
FEV1/FVC	Annual Spirometry	Reading [xx] + Date
FEV1	Annual Spirometry at 1yr after TDI-induced Asthma Diagnosis	Reading [x.xx] + Date
FVC	Annual Spirometry at 1yr after TDI-induced Asthma Diagnosis	Reading [x.xx] + Date
FEV1/FVC	Annual Spirometry at 1yr after TDI-induced Asthma Diagnosis	Reading [xx] + Date

Epidemiological (Aim 4 and Hypothesis 4)

This aim relates to determining as accurately as possible the annual incidence of TDI-induced asthma in TDI production environments. The specific hypothesis corresponding to this aim is that the annual incidence of TDI-induced asthma is well under 1% provided TDI workplace concentrations are maintained below ACGIH recommendations and there is a rigorous clinical work-up of potential cases.

Data Element Description	Source of Data	Form of Data
Study Entrance Date	Intake Questionnaire	Date
Classification of consistent with TDI-induced asthma	Work-up Classification: Completed by Consulting Pulmonologist	Yes/No/ Indeterminate + Date
Classification of consistent with work-related asthma	Work-up Classification: Completed by Consulting Pulmonologist	Yes/No/ Indeterminate + Date
Symptoms onset date	Intake or Periodic Questionnaire	Date
Last Date of Observation	Periodic Questionnaire	Date
Full shift TDI TWA by SEG, site, and time period adjusted	IH monitoring Data Collection Form TWA	TWA concentration + Respirator status during

Data Element Description	Source of Data	Form of Data
for respirator use	sampling	sampling + Date
HPET-specific TDI concentration adjusted for respirator use	IH Monitoring Data Collection Form STEL sampling	TDI concentration+ Respirator status during sampling + date

Epidemiological (Aim 5 and Hypothesis 5)

This aim relates to determining the likelihood that work-related asthma occurrences in the TDI manufacturing environment are associated with non-routine exposures to TDI or other agents. The specific hypothesis is that the majority of TDI-induced asthma cases will be associated with non-routine exposure episodes.

Data Element Description	Source of Data	Form of Data
Classification of consistent with TDI-induced asthma	Work-up Classification: Completed by Consulting Pulmonologist	Yes/No/ Indeterminate + Date
Classification of consistent with work-related asthma	Work-up Classification: Completed by Consulting Pulmonologist	Yes/No/ Indeterminate + Date
Full shift TDI TWA by SEG, site, and time period adjusted for respirator use	IH Monitoring Data Collection form TWA	TWA concentration + Respirator status during sampling + Date
HPET frequency by SEG adjusted for differences in TDI concentration	IH Monitoring Data Collection Form + HPET Frequency Form	TDI concentration + respirator status during sampling + Date
Presence of Acute Inhalation per worksheet	Acute inhalation worksheet	Date of incident
Reason for visit	Clinical encounter	Post-exposure incident, Date, Agent, presence of any respiratory symptom

Epidemiological (Aim 6 and Hypothesis 6)

This aim relates to assessing the effectiveness of the combined industrial hygiene and medical surveillance in preserving long-term pulmonary health. The specific hypothesis is that two key lung function parameters, FVC and FEV1, will show no greater rate of annual decline than that observed for comparable members of the U.S. general population.

Data Element Description	Source of Data	Form of Data
FEV1	Annual Spirometry	Reading [x.xx] + Date
FVC	Annual Spirometry	Reading [x.xx] + Date
FEV1/FVC	Annual Spirometry	Reading [xx] + Date
Birth date	Registration	Date
Height	Intake + Periodic	Reading [x.xx meters] +

	Questionnaire	Date
Weight	Intake + Periodic Questionnaire	Reading [xxx.x kgs] + Date
Gender	Intake Questionnaire	M/F
Ethnicity	Intake Questionnaire	White/Black/Other
Pack Years Smoked Cigarettes	Intake + Periodic Questionnaire	Calculated [xx] + Date
Technician and site	Spirometry file	Technician and site
Full shift TDI TWA by SEG, site, and time period adjusted for respirator use	IH monitoring Data Collection Form TWA	TWA concentration [xx.x ppb] + Respirator status during sampling + Date
HPET frequency by SEG adjusted for differences in TDI concentration	IH Monitoring Data Collection Form + HPET Frequency Form	TDI concentration over less than 30 minutes+ Date
Past medical history	Intake Questionnaire	MD diagnosed asthma, COPD, emphysema, pneumonia
Classification of consistent with TDI-induced asthma	Work-up Classification: Completed by Consulting Pulmonologist	Yes/No/ Indeterminate + Date
Classification of consistent with work-related asthma	Work-up Classification: Completed by Consulting Pulmonologist	Yes/No/ Indeterminate + Date

2. Selection of statistical methods:

To address the aims and hypotheses of this study, we will rely on two types of statistical analyses, descriptive and inferential. Descriptive analyses will be used to characterize the general findings of the study with regard to the aims and hypotheses and inferential analyses will be used to test the specific hypotheses addressed in the study. The methods of analysis are described below with emphasis on the methods to be utilized in testing specific hypotheses.

Where appropriate, initial regression diagnostics will be done. These can include determining the correlations among various explanatory variables to be considered in regression models. Regression diagnostics will also be used to test lack of fit and/or the appropriateness of general linear regression model: test for linearity, normality of residuals and homogeneity of variance. In addition, residual analysis will be used to test for influential observations and outliers as well as testing for lack of fit. Univariate analysis (means and standard deviations for continuous and frequency for categorical data) will be completed on all variables to be entered into the model to determine if transformation is necessary.

Medical Surveillance (Aim 1 and Hypothesis 1)

The two key outcomes with respect to this aim are participation rates in various aspects of the medical surveillance program and efficiency ratios defined as a ratio of the effective or useful output of a system to the total input. In the present context, we will be measuring the effectiveness of using a staged medical monitoring protocol to avoid subjecting employees to unwarranted testing. Two

measures of participation are defined under Section II .C. of the protocol, namely initial participation and full participation. Two efficiency measures are: 1) the ratio of TDI-induced asthma cases specifically identified through the screening program to the total accepted TDI-induced asthma cases identified by any means and 2) the ratio of employees subjected to Stage II and Stage III work-ups to total accepted cases based on the consultant pulmonologist review. These efficiency measures will also be determined for the outcome: work-related asthma as specified in the Work-up Classification: Completed by Consulting Pulmonologist

Initial and full participation rates will be characterized by gender, age, tenure, ethnicity, contractor status, and SEG at baseline of subject and by year of study using categorical methods (e.g., PROC FREQ in SAS). The denominators for the two efficiency ratio measures are apt to be relatively small; thus, the potential for analysis with respect to other variables may be limited. For each outcome variable, 95% confidence limits will be calculated and compared to the a priori hypotheses.

Medical Surveillance (Aim 2 and Hypothesis 2)

The positive predicted value will be calculated. The predictive value of a positive test is defined as the number of true positives divided by the number of true positives plus false positives. The predictive value of a negative test is the number of true negatives divided by the true negatives plus false negatives. The predictive values of individual questionnaire items and combined items will be determined in relation to the study asthma classifications.

Medical Surveillance (Aim 3 and Hypothesis 3)

Participants will be categorized as either having less than six months of symptomatic exposure or more than or equal to six months of symptomatic exposure. Symptoms and spirometry results collected on their last Periodic Questionnaire before transfer out of TDI work area will be compared to comparable data collected in subsequent years to assess change in symptom status and rate of decline of FEV1. Changes in continuous outcomes will be tested using linear mixed models (e.g. PROC MIXED in SAS). Chi-square analysis will be used to test dichotomous variables.

Epidemiological (Aim 4 and Hypothesis 4)

This hypothesis will be tested in two phases. First, there will be a determination that the TDI production environment is within ACGIH guidelines. Agreement with guidelines will be established by comparing annual SEG-specific and overall TWA and task-based short-term sample levels to ACGIH levels. To account for the use of respiratory protection as specified on the IH Monitoring Data Collection Form, the SEG TWA and task-based samples will be adjusted by an assigned respiratory protection factor.

Second, both average and cumulative annual incidence rates will be calculated for the following asthma categories: consistent with TDI-related asthma, consistent with work-related asthma, and indeterminate for work-related asthma. For those who are not classified in an asthma category, person-

years will be calculated from date of Intake Questionnaire to date of last Periodic Questionnaire where no symptoms were reported. For those who are classified into an asthma category, person-years will be defined as time from date of Intake Questionnaire to date of symptom onset as per the earliest report by Intake, Periodic, or Second-tier Questionnaire or TDI Clinical Encounter Template, 95% confidence intervals will be calculated for the estimated incidence rates.

Epidemiological (Aim 5 and Hypothesis 5)

The two key outcome variables with respect to this hypothesis are the occurrence of cases consistent with TDI-induced asthma and cases consistent with work-related asthma as classified by the expert pulmonary consultant. The primary explanatory factors of interest are 1) prior incidents of acute inhalation exposure, 2) relative frequency of performing HPETs at the time of case identification and mean full-shift TDI TWA at the time of case identification. Cases will also be characterized by gender, age, and duration of prior assignment to the unit relative to non-cases. In addition to descriptive analyses, a Cox proportional hazard model approach (PROC PHREG in SAS) will be utilized to determine if any of these factors are significantly predictive of case status. This analysis allows assessment of the instantaneous hazard at the time of each case occurrence and accumulates evidence of an effect across all case occurrences.

Epidemiological (Aim 6 and Hypothesis 6)

Statistical analysis of the longitudinal lung function data (FVC, FEV1, and FEV1/FVC) will be examined using a mixed effects model approach examining exposure levels and potential for peak exposures while controlling for potential confounding factors for lung function using the variables specified in the protocol section on selection of variables for hypothesis 6. Linear regression will also be used in a cross-sectional analysis at baseline and final test using the same exposure and potential confounders.

F. Rationale for Interpretation of Results

Hypotheses 1 through 3 are descriptive in nature. The testing of these hypotheses will be used to plan future studies. These descriptive analyses will appear in the final report and could serve as a basis for planning future studies.

Hypotheses 4, 5 and 6 are dependent in part on diagnosing asthma, work-related asthma and TDI-induced asthma. However, findings in these hypotheses will have to be put into perspective since we are not actually measuring “TDI-induced asthma” but rather asthma “consistent with TDI-induced asthma.” Thus, it will be necessary to discuss the potential errors in the classifications and how the findings could be affected as a result of misclassification.

A potential limitation of this investigation lies in the number of workers available for study, which will only be known in the early stages of the research and the prevalence of TDI-induced asthma. Nevertheless, this study attempts to include all current TDI production workers in the United States and will attempt to diagnose all TDI-induced asthma cases in these workers. Useful data could be diminished if few workers are actually exposed or if the exposed workforce experiences substantial

attrition. Although the study group hasn't been rigorously defined yet, preliminary data suggest that about 150 workers across four plants are eligible for this study. It is not yet known how many of these TDI workers will participate, but high participation is necessary to assure a credible study with sufficient power to detect potential effects since we assume that TDI-induced asthma is relatively rare. Before statistical analysis begins, investigators will judge if there are sufficient data to proceed with the analyses proposed above. If insufficient numbers of workers in the study preclude a credible analysis, consideration will be given to extending the time of the study. Even if no cases of TDI-induced asthma are observed in workers volunteering for this study, the study results will provide useful scientific information on the rate of TDI-induced asthma risk, albeit 0.0, in current workers .

The design of this study is in accordance with current literature, so the study can contribute to a general body of comparable information. The use of a classification of asthma and TDI-induced asthma by an expert are generally accepted for measuring the presence of asthma in epidemiology studies. While pulmonary function testing is not thought to be predictive of early stages of asthma, it has been useful for describing decline in lung function attributable to occupational exposures.

The power to detect statistically significant risks has not been calculated because no longitudinal change data have yet been measured in this workforce. Reports of TDI-induced asthma and average annual loss in lung function in the literature vary widely and are highly dependent on the testing protocol used and the level of exposure to TDI experienced. Nevertheless, we recognize that the TDI workforce is limited and exposures likely very low, so it is not expected that this investigation will have substantial power. On the other hand, longitudinal change is a relatively sensitive effect measure, which increases the value of even small amounts of data. Moreover, the compilation of results from a number of small studies can result in a substantial contribution when properly evaluated. Lastly, this effort can be seen as a way to prepare for longer follow-up investigations in the future.

G. Limitations

Although care has been taken to assure the validity and accuracy of the data that will be collected, the study design, as described in this protocol has a number of limitations, which will tend to reduce the likelihood of successfully achieving the aims. The power of the study is necessarily limited by the actual size of the population of potential participants, and the expected low frequency of the target health outcomes. Additionally, a number of potentially exposed individuals who do experience target health outcomes may not be determinable due to collection of insufficient information, the indeterminate nature of some of the findings, and incomplete participation in aspects of the study and medical protocol. Evaluation of hypothesis 3 will be limited by the frequency of routine data collection (annual). This hypothesis states that “Implementation of the Program will result in no more than six months of symptomatic exposure for any case of TDI-induced asthma and a complete cessation of asthma-related findings within one year of case detection.”

Aim 4 states “Determine as accurately as possible the annual incidence of cases consistent with TDI-induced asthma in the TDI production environments that are compliant with current occupational exposure limits and accepted industrial hygiene practice.” Achievement of this aim will be limited by a number of factors. Ascertainment bias may occur if some individuals with TDI-induced asthma are lost to follow-up for a variety of reasons, or the available medical data are insufficient for the medical consultant to categorize them. Differential participation due to variable inclusion of individuals in different risk categories at the participating facilities may result in reporting biases, which will be

difficult to detect and take into account. This may be due to variation in participation among individuals with different risks at different sites, as well as the varying roles and participation eligibility of contract employees at different facilities. The former will reduce the power of the study, but may be taken into account during analysis, while the effect of the latter issue on the observed incidence will remain difficult to determine.

Aim 5 is to "Assess the likelihood that work-related asthma occurrences in the TDI manufacturing environment are associated with non-routine exposures to TDI or other agents." An extensive sampling program is being undertaken, but accomplishment of this aim will be made more difficult by the complexity of the task of recognizing and determining exposures during upset conditions and other situations with potential for high exposures, as well as the deficiency of specific knowledge of the most appropriate metrics for risk of the development of TDI asthma. Many of the samples that will be available are planned to be time-weighted average exposures, which may not closely reflect the risk for TDI asthma.

III. Study Conduct

A. Recruitment and Enrollment Process

Recruitment and enrollment of participants will begin after 1) satisfactory completion of training of field personnel, 2) verification of field medical and environmental data collection, transfer, audit, and feedback procedures, and 3) approvals have been received from the ICG for all Statements of Work, and from the Human Studies Review Boards for this protocol. Initial recruitment and enrollment will begin simultaneously at all facilities and will be based upon the involvement and concurrence of the ICG in the content and process of recruitment. Enrollment of all participants present during the baseline recruitment will take place within six months of project initiation. After initial recruitment is completed, an assessment of the success of recruitment, and modification of procedures, as needed, will be based upon the results of information collected during the first three months after project initiation. A follow-up targeted and individualized recruitment for all non-participating employees and any new hires will be performed during the first two project years. Full participation will be defined as completing the participation and consent forms, the Intake Questionnaire and spirometry, and a Periodic Questionnaire within six months after the end of employment in the unit or the end of the study, as well as participating in the Stage I and Stage II protocols when requested. Refusal to answer specific questions or to participate in specific tests in the medical protocols will not be counted as non-participation. Project management reports will be submitted to the ICG every six months throughout data acquisition. The reports will highlight participation of eligible employees by plant and deviations from the exposure assessment and medical surveillance protocols.

A recommendation to the ICG regarding closure of the cohort will be made by the Medical Surveillance Task Group after evaluating the enrollment reports from the first two years.

B. Medical Monitoring Procedures

The data collected during application of the staged medical protocol, and the forms used to assess this data, will assist the responsible clinician in medical diagnostic and management determinations. The clinical interpretation of results of the medical evaluations for each participant is based entirely upon best medical judgment of the responsible provider, according to usual standards of care. Individual

medical management, including treatment and restriction of exposures, will take into account project-related results, but is performed completely independently of any project activities.

C. Emergency Procedures

In the event of an emergency due to the medical procedures in this protocol, standard procedures at each participating site will be followed (See Appendix 34).

D. Data Storage and Handling

The security of individual participants' identifying data is a significant and sensitive issue. Names are not sufficiently consistent to use in a data system for identification of participants. Social Security Numbers have been frequently used. However, with increasing attention in the U.S. to the problem of identity theft, another method is needed. The combination of the participant's date of birth and a check digit will be used to uniquely identify participants.

This participant ID number will only be used at the plant site, and the data management contractor will substitute an unidentifiable coded number in the database for the participant ID. After the study completion, no information will be retained that could link personal identifiers such as date of birth to the code numbers.

1. NIOSH

Spirometry data will be transferred to NIOSH for quality checks via the internet in a zipped file to a secure file transfer process site on the CDC Atlanta computer. Alternatively, zipped and password protected spirometry data files will be transmitted via email, or via a secure, tracked courier service or U.S. Express mail. The site offers different password-protected folders for each plant. All files transmitted between the satellite and quality control computers are compressed and password protected. A unique password is assigned to each file and is automatically generated by the satellite and quality control computer.

The program data with personal identifiers will be available to only those NIOSH personnel who are completing quality assurance checks. The data will be kept on a designated computer drive and will be password protected. Any paper, CD, or electronic copies will be kept locked up until destroyed as described elsewhere. The locked data sets with no personal identifiers are the only data sets that will be archived as a federal record.

2. ACC Diisocyanates Panel

Data management design for this study excludes the Diisocyanates Panel from receipt of data that identifies individual participants or plants. The Data Management Vendor (see below) will assure that the Diisocyanates Panel receives only data with personal and plant identifiers removed.

3. Data Management Vendor

Confidentiality policies for the data management vendor are shown in the contract, Appendix 40.

4. Data Access

a. Locking and releasing data sets for analysis

The DMTG will only release data in response to written instructions from the ICG. Those instructions should contain the limiting parameters (e.g. test < mm/dd/yyyy) and a list to whom the data should be sent. Released data will come from locked versions of the study database with personal and plant identifiers redacted.

The data management vendor will be responsible for generation of data sets released for analysis. The data will be provided in a read-only form on a CD-R. Copies of releases will be provided simultaneously to NIOSH and the ACC Diisocyanate Panel Manager. One copy will also be maintained throughout the life of the project by the vendor. Therefore, at least three copies of datasets will be provided in a read-only medium with each release of data for analysis.

b. Use of Data

The data provided to researchers for analysis will only be used to examine the hypotheses outlined in this protocol or subsequently approved by the ICG. Upon completion of the analyses of the protocol and approved hypotheses, all log files and output files will be archived to allow auditors to validate the analyses presented in the final reports. Should further analysis be required because of some study findings, these additional analyses must be outlined in a protocol for review by the ICG. Once the protocol has been approved, the procedures outlined above, will be followed.

c. Archiving/Data Retention and Destruction

NIOSH and the data management vendor will protect confidential information by using it for the least amount of time possible for quality assurance checks, and then destroying that information in a manner consistent with confidential information, i.e. paper records and CDs will be destroyed; computer records will be deleted so that they cannot be reconstructed. Only study data transmitted from the data management vendor, as the locked datasets will be archived according to Division of Respiratory Disease Studies (DRDS), NIOSH procedures.

The data management vendor will supply NIOSH with the necessary information and documents for compliance with DRDS requirements. These include the important project documents such as the data dictionary to be included in the file along with project data. The database must be saved with its source code. An ASCII text file describing the raw data, its file structures, the processing programs, order of execution, and other details necessary to create the output data sets should be stored with these files. The text file should clearly describe how the output data files can be accessed and analyzed. A copy of the DRDS Data Management and Archiving Manual is included as Appendix 31. Other important documents such as copies of the MOU, Statements of Work, meeting minutes, etc. will be archived by ACC.

E. Human subjects

Informed consent will be obtained (see Consent forms in Appendices 17 and 18).

Individual medical management, including treatment and restriction of exposures, will take into account project-related results, but is performed completely independently of any project activities.

Study participants will be informed of individual test results within 30 days of test completion.

F. Quality Assurance and Archiving

1. Data Quality Strategy

All data submitted for entry into the database will be subject to data quality verification. When possible, automated processes will be utilized. Forms and data files that fail data quality checks will be returned to the source as soon as is practicable for correction and re-submission.

Successful submission of data that passes established quality checks will be the responsibility of the submitting health care professional or industrial hygienist. Participating nurses and industrial hygienists will be provided the details of these data quality checks so they are fully informed of the details of data quality expectations. Submissions that fail data quality checks and are returned for correction, but are never re-submitted will be considered delinquent.

Neither the data management vendor nor the DMTG will assume responsibility for submission of the data required by the study protocol. That responsibility will reside with the participating companies and the responsible environmental health and safety professionals for each company. Neither the Vendor nor the DMTG will pursue compliance with the protocol by plant medical or industrial hygiene staffs. The responsible EH&S professionals will be supported by exception reports produced by the data management vendor. These reports will highlight variances from the study protocol, e.g. missing or late medical surveillance questionnaires from participating employees or insufficient numbers of air sample measurements for SEG.

Only data for previously registered employees and SEGs will be accepted. Forms and data files submitted for other people and undefined SEGs will be returned to the source. If these submissions are correct, the submitting nurse or industrial hygienist will need to submit a registration form for the person or SEG before the forms and files can be accepted by the data management vendor.

In consultation with the other task groups, the DMTG will provide the data management vendor with the following information for each data element.

- Whether a valid entry is required for acceptance of the form or data file.
- Range of acceptable entries, e.g. limits of possible entries.
- Whether the entry must be confirmed by lookup in a reference table, e.g. personal identifiers.
- How acceptable entries will be stored in the data file.
- How missing values are to be recorded in the data file.

A study identification number will be used to assure that the identity of individuals will not be revealed. The data management contactor will maintain the sole master list which identifies the study identification number with individual identifying information. This master list will be not be shared with anyone outside the contract group. Upon completion of the study, the master list will be destroyed by the contractor.

The data contractor will be the sole final repository of all study data. All intermediate results collected by study investigators will be forwarded to the data contactor. All intermediate results will be destroyed once stored by the data management contractor unless there is a legal requirement to maintain this information or if this information has been identified as necessary for future quality control audits.

2. Quality Assurance Methods – Exposure Assessment

All individuals involved in exposure monitoring for this study will receive training to ensure uniform data collection and documentation. The DMTG will provide feedback to individual sites and the ICG when deviations in collection and documentation occur. Site personnel will periodically review exposure assessment protocols and procedures to assure all data meets specifications. NIOSH will conduct quality control visits to observe exposure data collection on an annual basis and more frequently as resources permit.

a. TDI badge and optical reader

The badge manufacturer will retain their current quality assurance/quality control procedures and will include the newly developed Optical Reader. In addition, the field validation of the badge with the Optical Reader will contribute to the assurance the badge is performing properly under industrial conditions. The manufacturer will provide a mechanism or procedure for assuring a control or blank badge value is subtracted from the actual reading. A calibration reference card will be used to provide periodic calibration of the instrument. Manufacturer's recommendations for use will be followed.

b. Coordinating Exposure Monitoring

The activities for the industrial hygienist coordinating the exposure monitoring efforts are listed below. The plant industrial hygienist:

1) is the person in charge of administering the TDI exposure monitoring. He/she will train employees who will assist in the sampling to ensure uniformity of procedures and adherence to the protocol. Part of the training will include training on badge collection, the optical reader, placement of badge within the breathing zone of the worker, and reading of the badge.
2) will issue a schedule that assures random sampling. When a sample schedule cannot be followed (inclement weather, workload of employee cannot accommodate exposure monitoring schedule, etc...) the Industrial Hygienist will work with employees to ensure data is collected at first available opportunity following the missed exposure assessment.
3) will design a data collection system that ensures exposure monitoring will be collected as prescribed. Exposure monitoring records will be audited by the Industrial Hygienist as proof of complete and accurate data collection. The Industrial Hygienist will take part in the exposure monitoring effort as often as time permits. The Industrial Hygienist will oversee HPETs involving respiratory protection to ensure *potential* exposures (respiratory protection used) are captured in addition to *actual* exposures.
4) will direct the activities of others to include badge reading using the optical reader within 24 hours of sampling (preferably immediately after sampling).
5) will coordinate activities with medical personnel also working on the project.

3. Quality Assurance Methods – Medical Monitoring

A continuous process of quality assurance and auditing will be established. All medical data will be transmitted to the data management contractor within five working days of collection. The contractor will forward the data to the NIOSH quality assurance personnel within two working days. Review for quality and completeness, based upon accepted professional recommendations, will be performed within an additional five working days, and a specific report for each participant returned to the originating medical department. Quality assurance statistics tabulated by site and overall will be reported quarterly to the Medical Surveillance Task Group throughout the project.

When performance of a series of flow measurements is requested, quality assurance will be performed based upon the results transmitted to NIOSH during the twice weekly medical department visits. Quality feedback reports will be returned within one week to the originating medical department.

NIOSH will perform training of all medical data collection personnel. Training will include satisfactory completion of a NIOSH-provided training course, including a final practical and written examination. Additional updates will be performed, based upon the results of ongoing quality assurance reporting, and will include site-specific feedback and individual observations. NIOSH will conduct quality control visits to observe medical data collection on an annual basis and more frequently as resources permit.

a. Forms Data

Data entry edits will be developed by the DMTG in consultation with the other task groups. These include specification of mandatory fields for acceptance of forms submitted. These data entry edit specifications will be provided to the data management vendor. The data management vendor will incorporate the data entry edit parameters into the data dictionary. These parameters will become a permanent document of the project.

NIOSH personnel will be able to conduct quality assurance checks for all forms submitted. Electronic images of the forms entered into the database will be sent to NIOSH on a monthly basis along with a copy of the temporary, data entry database. The data management vendor will be responsible for monitoring completeness and clarity of forms submitted and for returning deficient forms to the source for correction and re-submission.

NIOSH personnel will compare digitized images of submitted forms with the data entry database. Any questionable entries will be referred back to the vendor and the DMTG. Logs will be kept of the number and types of mistakes found so that the data collection process can be improved. DMTG will provide feedback to the vendor and the ICG as part of the continuous quality improvement process.

b. Outpatient Spirometry Data

All outpatient spirograms will be sent via the FTP site to NIOSH for a quality control review. The quality control software will automatically assign a grade from A to F for each test session based on repeatability and other criteria. All spirograms will be reviewed by NIOSH personnel. In some cases, a new spirometry examination may be requested. After this review, all spirograms will be forwarded to the data management vendor in a standard file format acceptable to the vendor. The FVC and FEV1

quality control codes for each spirogram will be included in the data files sent to the data management vendor. Feedback reports will be sent to the medical personnel at the plant sites.

The DMTG will work with the Medical Surveillance and Data Analysis Task Groups to establish criteria for the quality control review. The Spirometry Quality Control Program is attached. The review criteria are shown in Appendix 26.

c. Self-Administered Portable Spirometry Data

Self-administered portable spirometry data will be downloaded onto the NIOSH-supplied laptops at the site. The report will be transmitted to NIOSH for a quality check. The transmission will be through the FTP site, by disk, or by modem. NIOSH will perform a quality check on the spirograms including a review of all curves. The quality check will include checks for the number of efforts performed per day and number of hours covered as specified by the Medical Surveillance Task Group. After the check, all data will be transmitted to the vendor for inclusion in the database. Quality Control Reports and requests for retesting will be sent back to the plant sites, as required.

The output report sent to the vendor will be in a standard file format with FEV1, FEV6, FEV1/FEV6, FVC, FEV1/FVC, PEF, pre-post % change, variability, and quality grades plus a set of questions that is programmable by NIOSH personnel. The report will contain one file for each test session with the three best spirometry tests. To plot the curves, the file contains one hundred (100) coordinates for the y-axis and the x-axis is a standard interval.

The DMTG will work with the Medical Surveillance and Data Analysis Task Groups to establish criteria for the quality control review. Evaluation criteria are incorporated in the serial flow data interpretation form.

4. Study audits by Scientific Peer Review Panel

An audit of this study occurs, at a minimum, two times during its course. The Scientific Peer Review Group is comprised of epidemiologists and other scientists with appropriate expertise not on the study team and is selected by agreement of the ICG. The first mandatory audit takes place after the principal authors have received and incorporated the review comments of the components of the draft final report from the co-investigators and the ICG. This initial audit takes place after these initial comments are received by the principal investigator but prior to final approval of the co-investigators and the ICG. The second mandatory occurrence of the audit process takes place upon completion of the review and approval of the draft report by all co-investigators and the ICG. The second audit may be performed through the Scientific Peer Review Group, through a peer-reviewed journal, or by another independent peer review mechanism, at the option of the ICG. The ICG can also initiate other audits if requested by a co-investigator. For example, if considerable effort is required to develop a database for a research study, the quality of the data can be audited prior to any analysis. Similarly, the analysis can be audited prior to the writing of a draft final report.

The audit will determine the following:

- Are the methods described in the draft final report identical to those of the study protocol? If not, are there addenda attached to the study protocol to explain the differences? The study addenda must be approved by the principal investigator, co-investigators, and, if they are major or could impact the health of the study subjects, the Human Subjects Review Board.

- Are there typographical errors in the draft final report?
- Are there any inconsistencies in the draft final report as to what is said in the text and what is found in the tables?
- Are all cited references listed in the reference section? Are all listed references cited in the draft final report?
- Does the last page of the draft final report contain an archiving statement?
- Are all computer programs used in data analyses as well as their output appropriately labeled and available for review? Internal program documentation must be provided for all user written programs (e.g. SAS programs). The principal authors must also provide a written index that relates the data presented in the draft final report to the computer outputs. If deemed necessary, the auditors may randomly select data reported in the final report (data reported in the text or tables) to determine whether the index allows for an adequate basis to trace the data back to the original computer output.

If there is cause for concern about the data integrity, the auditors may also randomly select data from the draft final report to verify that the reported data concur with the computer printouts/analyses. Upon approval of the draft final report by all parties, the study is complete, the report becomes final and the principal investigator assures that the study file is archived. Permanent records of all other data generated during the course of this study are subject to privacy and confidentiality considerations. All data gathered or generated, including protocol addenda and the final report, will be archived according to standard procedures of the member companies or NIOSH.

G. Communications

1. External Communication

Mandatory reporting requirements arise when there exists either (1) a "substantial risk of injury to health or the environment" under TSCA § 8(e); or (2) an adverse effect on the environment or public health under FIFRA § 6(a)(2). Reporting law is the responsibility of the participating companies. However, the ICG may decide to report findings under these laws also.

The ICG recognizes that member companies have a time sensitive obligation to report findings, results, conclusions, or opinions indicating either: (1) a "substantial risk of injury to health or the environment" under TSCA § 8(e); or (2) an adverse effect on the environment or public health under FIFRA § 6(a)(2). If NIOSH or other program staff discover any findings, results, or opinions indicating either a "substantial risk of injury" or an "adverse effect" during the course of the Study, they agree to notify the panel manager immediately by telephone, provide a facsimile detailing the essential data within 24 hours, and provide a follow-up letter within four working days. The panel manager will then promptly notify each participating company representative so they can assess the reportability of the findings.

Other than mandatory reporting requirements, no external communication will take place until all study subjects have been informed of their individual findings and any specific findings of the study. The ICG, in consultation with the Scientific Peer Review Panel and the study investigators, will approve all external reports. The external reports will include at a minimum a final report which addresses all the study hypotheses, and one or more papers submitted for publication in a peer reviewed scientific journal.

2. Internal Communication

During the initial communication about the project with employees at each site, the importance of voluntary participation is emphasized (see Appendix 38).

Study subjects will be informed of all their individual test results within 30 days of the availability of the results and will be provided an opportunity to discuss these findings with a health care professional, utilizing company medical department staff according to the policies and procedures now in place at each plant. Within 60 days of completion of an interim or final report, the study subjects will be informed and provided a copy of the findings.

Individual participating facilities will arrange for the most convenient method for delivering interim report findings with participating employee groups and other stakeholders. An opportunity will be provided for study participants to provide feedback on the medical surveillance, data collection and exposure monitoring processes.

To collect feedback from study participants, an anonymous and confidential monitoring evaluation form will be distributed to workers on an annual basis to evaluate medical and exposure monitoring. The Evaluation Questionnaire will be one page and will be given to participants with a stamped addressed envelope. These forms will be returned by mail to the study contractor for analysis on a yearly basis

H. Outside Contract Personnel

The DMTG will assign a person as liaison to the data management and forms design vendors. The liaison will receive vendor questions. Site and vendor personnel will make an attempt to solve any problems themselves; however, a log should be kept of all problems. This log will be included in the project management reports provided to the DMTG on a quarterly basis. Suggestions for process changes may be made by the DMTG. Any problems that cannot be resolved between vendor and site personnel or recurring problems should be referred to the liaison for further action. The liaison will refer the problem to the DMTG and the respective company's representative for corrective action. If still unresolved, the matter will be referred to the ICG.

The liaison will receive vendor questions. The liaison may consult with other task group members to find an answer. If the question cannot be resolved by the DMTG, it will be referred to the ICG.

I. Resources

1. Training of site medical and industrial hygiene personnel in protocol requirements.

Prior to the implementation of site data collection, training will be conducted for those plant personnel who will be involved in this collection process. The training should be conducted at a location mutually agreeable to NIOSH and the participating plants. The purpose of the training is to ensure consistent data collection across all four sites. Plant personnel are very experienced in performing their day-to-day jobs; however, the study protocol will require staff to operate in a slightly different mode than they normally operate. Therefore, the situation necessitates universal training to eliminate inconsistencies in data collection and reporting, to the maximum extent possible. Plant personnel involved in the study who are added during the study will receive the same training.

For medical staff, training will include:

- Review of study protocol as it pertains to staging of medical evaluations.
- Instruction on completion of staged medical questionnaires and submission to the vendor.
- Familiarization training with the various spirometers to be used in the study protocol; includes overview of equipment and software, features of the NIOSH spirometry system, the examination protocol, quality control, and spirogram submission procedures to NIOSH.
- Review of NIOSH process to provide direct quality control feedback to individual sites.

For industrial hygiene staff, training will include:

- Review of study protocol as it pertains to collection, documentation, and submission of exposure monitoring data.
- Review of exposure monitoring methods to be used in study protocol.
- Instruction on completion of routine and incident exposure monitoring data and submission to the vendor.
- Review of NIOSH process to provide direct quality control feedback to individual sites.

2. Spirometry Equipment

All clinic sites will use the same type of spirometry equipment and NIOSH will assure that all personnel performing the tests receive initial training. (See project procedures manual)

IV. REFERENCES

Baur X, Huber H, Degens PO, Allmers H, Ammon J. Relation between occupational asthma case history, bronchial methacholine challenge, and specific challenge test in patients with suspected occupational asthma. *Am J Ind Med* 33:114-122, 1998a.

Baur X, Chen Z, Liebers V. Exposure-response relationships of occupational inhalative allergens. *Clin Exp allergy* 28(5):537-544, 1998b.

Bernstein DI, Jolly A. Current diagnostic methods for diisocyanate induced occupational asthma. *Am J Ind Med.* 36:459-468, 1999.

Bernstein IL, Chan-Yeung M, Malo J-L, Bernstein DI. Definition and classification of asthma. In Bernstein IL, Chan-Yeung M, Malo J-L, Bernstein DI, editors. *Asthma in the Workplace*. Marcel Dekker, Inc. New York, pp.1-4, 1993.

Bugler, J, Clark RL, Hill ID, McDermott M. The acute and long-term respiratory effects of aromatic di-isocyanates. A five year longitudinal study of polyurethane foam workers. III Report 10848. Manchester, U.K., International Isocyanate Institute, Inc. May, 1991.

Contreras GR, Rousseau R, Chan-Yeung M. Occupational respiratory diseases in British Columbia, Canada in 1991. *Occup Environ Med* 51:710-712, 1994.

Fuchs S, Valade P. Etude clinique et experimentale sur quelques cas d'intoxication par le Desmodur T. *Arch Mal Prof* 12:191-196, 1951.

Henneberger PK, Kreiss K, Rosenman KD, Reilly MJ, Chang Y-F, Geidenberger CA. An evaluation of the incidence of work-related asthma in the United States. *Int J Occup Environ Health* 5:1-8, 1999.

Jajosky RA, Harrison R, Reinisch F, Flattery J, Chan J, Tumpowsky C, Davis L, Reilly MJ, Rosenman KD, Kalinowski D, Stanbury M, Schill DP, Wood J. Surveillance of work-related asthma in selected U.S. states using surveillance guidelines for state health departments – California, Massachusetts, Michigan, and New Jersey, 1993-1995. *Mor Mortal Wkly Rep CDC Surveill Summ* 48(3):1-20, 1999.

Klees JE, Alexander M, Rempel D, Beckett W, Rubin R, Barnhart S, Balmes JR. Evaluation of a proposed NIOSH surveillance – Case definition for occupational asthma. *Chest* 98:212S-215S, 1990.

Malo J-L, Ghezzo H, L'Archevêque J, Lagier F, Perrin B, Cartier A. Is the clinical history a satisfactory means of diagnosing occupational asthma. *Am Rev Respir Dis* 143:528-532, 1991.

Malo J-L, Ghezzo H, Élie R. Occupational asthma caused by isocyanates. Patterns of asthmatic reactions to increasing day-to-day doses. *Am J Respir Crit Care Med*. 159:1879-1883, 1999.

Malo J-L, Chan-Yeung M. Occupational asthma. *J Allergy Clin Immunol* 108:317-328, 2001.

McDonald JC, Keynes HL, Meredith SK. Reported incidence of occupational asthma in the United Kingdom, 1989-97. *Occup Environ Med* 57:823-829, 2000.

Meredith SK, Nordman H. OA: measures of frequency from four countries. *Thorax* 51:435-440, 1996.

Meyer JD, Holt DL, Cherry NM, McDonald JC. SWORD '98: surveillance of work-related and occupational respiratory disease in the UK. *Occup Med*. 49:485-489, 1999.

Moscato G, Dellabianca A, Vinci G, Candura SM, Bossi MC. Toluene diisocyanate-induced asthma: Clinical findings and bronchial responsiveness studies in 113 exposed subjects with work-related respiratory symptoms. *J Occup Med* 33:720-725, 1991.

National Heart, Lung, and Blood Institute (NHLBI). Guidelines for the diagnosis and management of asthma. Expert Panel Report 2. Bethesda, MD, (NIH) Publ No. 97-4051, 1997.

National Institute for Occupational Safety and Health (NIOSH): Work-related lung disease surveillance report – 1994. DHHS (NIOSH) Publication No. 1994-120, NIOSH, Cincinnati, OH, 1994.

National Institute for Occupational Safety and Health (NIOSH): Work-related lung disease surveillance report – 1999. DHHS (NIOSH) Publication No. 2000-105, NIOSH, Cincinnati, OH, 2000.

National Institute for Occupational Safety and Health (NIOSH): Work-related lung disease surveillance report – 2002. DHHS (NIOSH) Publication No. 2003-111, NIOSH, Cincinnati, OH, 2003.

Nguyen B, Ghezzo H, Malo J-L, Gautrin D. Time course of onset of sensitization to common and occupational inhalants in apprentices. *J Allergy Clin Immunol* 111:807-12, 2003.

Nieuwenhuijsen MJ. Exposure assessment in occupational epidemiology: measuring present exposures with an example of a study of occupational asthma. *Int Arch Occup Environ Health*. 70:295-308, 1997.

Ott, MG, Klees JE, Poche SL. Respiratory health surveillance in a toluene di-isocyanate production unit, 1967-97 – Clinical observations and lung function analyses. *Occup Environ Med* 57:43-52, 2000.

Ott MG, Diller WF, Jolly AT. Respiratory effects of toluene diisocyanate in the workplace: A discussion of exposure-response relationships. *Crit Rev Toxicol* 33(1):1-59, 2003.

Paggiaro PL, Loi AM, Rossi O, Ferrante B, Pardi F, Roselli MG, Baschieri L. Follow-up study of patients with respiratory disease due to TDI. *Clin Allergy* 14:463-469, 1984.

Pisati G, Baruffini A, Zedda S. Toluene diisocyanate induced asthma: Outcome according to persistence or cessation of exposure. *Brit J Ind Med* 50(1):60-64, 1993.

Provencher S, Labrèche FP, De Guire L. Physician based surveillance system for occupational respiratory diseases: the experience of PROPULSE, Québec, Canada. *Occup Environ Med* 54:272-276, 1997.

Redlich CA, Karol MH. Diisocyanate asthma: clinical aspects and immunopathogenesis. *Int Immunopharmacol* 2(2-3):213-224, 2002.

Rosenberg N, Garnier R, Rousselin X, Mertz R, Gervais P. Clinical and socio-professional fate of isocyanate-induced asthma. *Clin Allergy* 17:55-61, 1987.

Ross DJ, Sallie BA, McDonald JC. SWORD ’94: Surveillance of work-related and occupational respiratory disease in the UK. *Occup Med* 45:175-178, 1995.

Saetta M, Di Stefano A, Maestrelli P, De Marzo N, Milani G, Pivirotto F, Mapp CE, Fabbri LM. Airway mucosal inflammation in occupational asthma induced by toluene diisocyanate. *Am Rev Respir Dis* 145:160-168, 1992.

Tarlo SM, Banks D, Liss G, Broder I. Outcome determinants for isocyanate induced occupational asthma among compensation claimants. *Occup Environ Med* 54:756-761, 1997.

Tarlo SM, Liss GM, Yeung KS. Changes in rates and severity of compensation claims for asthma due to diisocyanates: a possible effect of medical surveillance measures. *Occup Environ Med*. 59:58-62, 2002.

Tarlo SM, Liss GM. Diisocyanate-induced asthma: Diagnosis, prognosis, and effects of medical surveillance measures. *Appl Occup Envirom Hyg* 17 :902-908, 2002.

Weill H, Butcher B, Dharmarajan V, Glindmeyer H, Jones R, Carr J, O’Neil C, Salvaggio J. Respiratory and immunologic evaluation of isocyanate exposure in a new manufacturing plant. U.S. Dept of Health and Human Services, U.S. Government Printing Office, (NIOSH) Publication No. 81-125, Washington, D.C 1981.

Wisnewski AV, Redlich CA. Recent developments in diisocyanate asthma. *Curr Opin Allergy Clin Immunol* 1(2):169-175, 2001.

Woodbury JW. Asthmatic syndrome following exposure to toluene diisocyanate. *Ind Med Surg*. 25:540-543, 1956.